FASTING
AND UNDERNUTRITION

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A Biological and Sociological Study of Inanition

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NEW YORK
E. P. DUTTON & COMPANY
681 FIFTH AVENUE

Printed in the United States of America.

TO

PROFESSOR THOMAS HUNT MORGAN

THIS BOOK IS

GRATEFULLY AND RESPECTFULLY

DEDICATED BY

THE AUTHOR.

PREFACE

The truth has been early recognized that the metabolism during inanition is the starting point in all nutritional studies and that it must, therefore, be considered as the corner stone of any edifice of a theory of nutrition. The experimental investigation of fasting or inanition, apart from the far-reaching import which the problem presents, has long been a favorite method in the attack upon various nutritional questions. In fact, fasting as a method of study has been not infrequently used without full appreciation of the phenomenon of fasting. In the preparation of the present volume, which it is believed is filling a real need for a comprehensive survey of the subject, two definite objectives have been sought: first, to collect and to classify what is known about inanition; secondly, to consider the facts in their proper biological setting. The discovery of fundamental principles is, of course, of primary importance and this can best be served by a comparative study of all organisms, irrespective of the position which they occupy in the scale of evolution.

Fasting presupposes the absence of nutriment, but "nutriment" is here conceived in the same broad sense as was already done by Hippocrates who declared that "The body is sustained by three kinds of nutriment: food, drink, and air, of which the last is by far the most important." This statement expresses the truth with such clear-cut precision that to encompass the large content of our modern knowledge of nutrition this conception needs but slight revision. Fasting is, therefore, absence of all nutriment or of any particular kind of nutriment. Although the discussion centers about acute inanition, which is the most thoroughly investigated type of fasting, the attempt has been made to evaluate the influence of the different kinds of fasting and to determine their respective biological and sociological significance.

The problem of inanition is replete with human interest. As soon as one turns his attention to this subject many questions immediately arise: How far is inanition compatible with life?

How does the power of resistance to inanition differ in various organisms? How long can the normal state of the body be preserved and organic function maintained unimpaired during fasting? In what different ways does fasting influence the organism and how is death caused by it? It is no longer open to question that man, in common with other organisms, possesses the ability of enduring a protracted fast. Through misfortune or through disease, with suicidal intent or for experimental demonstration, human fasts of extremely long duration have occurred of which there are authentic records. But how does prolonged fasting affect hunger, pain and appetite? In spite of the testimony of fasters, the question is still far from being settled. If appetite and the sensation of hunger completely disappear, it is difficult to see why hunger sharpens the struggle for existence or why animals even after weeks of starvation consume food voraciously. Fasting certainly is not a fatal experience, but it is doubtful if it is either a pleasant or even a painless experience. The old saying "a hungry man is an angry man" unquestionably epitomizes poignantly mankind's acquired knowledge. Knut Hamsun, in his autobiographical book *Hunger*, has given by far the strongest artistic expression of this gruesome individual experience, while folklore of many lands or accounts in the Bible offer some of the most forcefully drawn pictures of the mass suffering in famines.

The greatest interest which fasting has always aroused springs neither from its biological nor from its sociological significance but from the fact that since time immemorial it has been thought to be the means of physical purification and of elimination of disease from the body. Fasting for health is very largely the sport of amateurs nowadays, but the therapeutic potentialities can be determined not by argumentation but by careful experimentation. There are a few instances of well-authenticated therapeutic value of fasting. Allen's starvation treatment of diabetes fully justified itself in the hands of expert practitioners and has been in vogue for a number of years; Aron finds in fasting the most potent agency in combating certain diseases of childhood; McCollum recently discovered that inanition has a beneficial effect on rickets which it shares with the ultra-violet ray or with the vitamin treatment. These are but very few positive results, but it would be unreasonable to suppose that they exhaust the therapeutic possibilities. At any rate, a broad knowledge of the

biology of inanition must form the foundation for its practical application.

A matter which deserves particular attention is the causation of disease by inanition. This, strictly speaking, is a chapter in practical medicine which still requires to be worked up. McCarrison in his book on *Deficiency Diseases* has made a brilliant beginning in that direction. The whole conception of inanition diseases, at least so far as diseases of children are concerned, has been recently very ably developed by Professor Hans Aron in an article in the *Ergebnisse der gesamte Medizin*, Bd. III. It is to be hoped that this aspect of inanition will receive further attention from clinicians.

In the preparation of the book I received generous aid and encouragement from many friends, too numerous to mention individually. It has been also my great privilege that parts of the manuscript were read through by Professor Walter B. Cannon, Professor A. P. Mathews and Professor Frank H. Pike, to whom I wish to express my gratitude for this friendly courtesy and for the valuable suggestions received from them. I am indebted to the editor of *The Scientific Monthly* for the permission to republish the introductory chapter. I am also indebted to Miss Elizabeth A. Leggett for her assistance in the preparation of the index and to our Librarian, Miss Madalene Hillis, for checking up a number of references. To the publishers, E. P. Dutton & Co., I beg to acknowledge my sincere appreciation of their effort and splendid spirit of coöperation in the production of the book.

S. MORGULIS.

Omaha, Nebraska,
February 23, 1923

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PART I

INTRODUCTION

INTRODUCTION

In a strict sense an organism experiences inanition whenever it subsists on material previously stored in its tissues. Such a contingency may be forced upon it by circumstances or may be embraced through a voluntary impulse. As a deliberate act of total abstinence from food, inanition possesses elements of dramatic effect. In primitive times it was a sign of miraculous and supernatural gifts attributed to the faster, shedding the glory of heroism on his deeds. Founders of religious movements were wont to fast for long periods, which doubtless enhanced their prestige for leadership and sanctified their commandments. As a biological phenomenon, however, inanition has little of either the spectacular or of the heroic, and as a sociological fact it is common and insidious in its effects.

It is erroneous to suppose that during inanition the processes of nutrition are interrupted. Obliged to exist wholly or in part on accumulated reserves contained in the tissues, the fasting organism is nourished just as truly as if it lived on the fat of the land. But now it is being nourished from within, not from without. Fed or starved, the living organism is governed rigorously by the law of conservation of energy. To maintain its body temperature, to perform vital functions (heart beat, respiration, secretion, etc.), to produce mental and physical effort the potential energy of food stuffs must be transformed into the various forms of kinetic energy. The organism cannot create either matter or energy, and failing to find this from without must use up its own potential energy. Every organism contains in its tissues a source of energy in the form of rich deposits of nutritive substances, which constitute the common foods when they serve to nourish another organism. Thanks to these large deposits, the existence of an organism is not readily endangered through abstinence. Since the metabolic processes obey the usual physical laws, inanition must be regarded as a special—perhaps, the simplest—form of nutrition.

The three chief objects of nutrition are to furnish matter for organic growth and repair of incidental wear and tear of

the tissues, to supply energy for maintenance, and energy for work. These objects are likewise attained under the conditions of inanition. Active growth and regeneration are not incompatible with inanition, and the wear and tear, at least in some organs, is so completely repaired as to evade for a long time the effect of a nutritional stringency. Inanition does not preclude the ability for extreme and sustained exertion.

According to the mode of origin we can distinguish three types of inanition. First, physiological inanition which is a normal, regular occurrence in nature. The inanition constitutes either a definite phase in the life cycle of the animal, it is a seasonal event, or it accompanies the periodic recurrence of sexual activity: next, pathological inanition of various degrees of severity associated with different organic derangements. It may result from some obstruction of the alimentary canal (œsophageal stricture), from an inability to retain food (vomiting), or from imperfect utilization owing to rapid elimination (diarrhea), from excessive destruction of body tissues (infectious fevers), or from refusal to take food either because of loss of appetite or mental disease. Considering the many variations of inanition possible, it is not venturesome to say that nearly every disease presents a case of pathological inanition. Finally, there are a number of instances of abstention which for convenience may be grouped under the designation of accidental or experimental inanition. In this category, of course, belong all individual experiences of fasting which have been the subject of carefully conducted scientific investigation. Indeed, our knowledge of inanition is derived almost exclusively from laboratory observations.

Under the condition of total abstinence the organism depends entirely upon its reserve material. This condition, however, is neither the most common nor the most important aspect of inanition. Profound alterations in the metabolic processes are occasioned when the organism is deprived of some peculiar —though quantitatively insignificant—component of the diet, or when the food fails to supply matter and energy according to the actual demands of the organism. In the last case, especially, the reserve deposits of the organism will be insidiously exhausted. It is obvious, therefore, that we must discriminate between complete, partial and chronic inanition.

When inanition assumes the proportions of a mass experience

we are no longer confronted with a purely biological phenomenon. Inanition becomes a sociological problem. The biology of inanition has the same significance for the sociological problem as the physiology of nutrition in general has for the economy of national feeding. The information gained from a study of the individual furnishes a most valuable basis for grasping the significance of the problem and serves as a dependable guide in the search of a rational solution. In either case, however, the sociological condition is not merely a multiplication or a summation of individual experiences. As a sociological phenomenon, therefore, inanition presents a distinct and much more complicated problem. One can not intelligently deal with this aspect of the problem unless the fundamental fact is grasped of the influence of the economic forces in grouping individuals into classes living under distinct, social environments.

As a physiological phenomenon, inanition is invariably of the type of complete abstinence, the nutritive deposits of the organism furnishing the only source of energy and matter. Animals which experience inanition periodically have developed, probably through adaptation, a tendency to acquire during the feeding season large stores of fat. Physiological inanition is frequently of very long duration for which a large supply of nourishment is indispensable. In hibernation, owing to the very low degree of metabolic activity, the nutrient deposits are used up sparingly, but physiological inanition may also be associated with vigorous activity.

Under pathological and accidental (experimental) conditions we encounter inanition in its numerous variations, ranging from total abstinence to some specific dietary deficiency. Chronic inanition, occasioned by the failure to balance properly the organism's demands and supplies, and partial inanition, determined by lack of some element vitally important for the normal functioning of the organism, both underlie many pathological states. A number of diseases have been traced in recent years to the want of specific substances in the diet, and these must be regarded as cases of partial inanition. Chronic inanition, on the other hand, is a common physical basis of many ills, like dyspepsia, general debility, loss of nervous stamina, depression and fatigability, neurasthenia, all of which flourish in the organism whose reserves have been persistently and insidiously sapped.

Strictly speaking, chronic and partial inanition are primarily laboratory occurrences. By this is meant that inanition of a definite type can only be produced generally under conditions amenable to experimental control. Inanition as a social phenomenon is, as a rule, neither simple nor clearly defined, though one meets such instances, too. In certain social strata it would be impossible to determine whether the population suffers from chronic or partial inanition in the sense attributed to these terms. Among our industrial population the earning capacity and the cost of provisions are not adjusted with the sole view of procuring for them the necessary quota of energy. This adjustment is left wholly to the precarious workings of the law of supply and demand of labor. It is proverbially true that this adjustment is neither quick nor prejudicial in favor of the economically dependent class. Chapin's report on the standard of living among workingmen's families gives ample evidence of widespread undernourishment. The actual conditions must be much worse than one gathers from the report because the undernourishment is calculated on the basis of food purchased. This method of calculation leaves out of consideration a very essential factor, namely, the nutritive quality of foods sold in the poor sections of our cities. Where parsimony cuts down on quantity it is practically certain that the dietary quality is likewise degraded. The result is a combination of chronic with partial inanition. From a sociological point of view total abstinence from food is practically unimportant, while the ever present and common partial and chronic inanition blend into the insidious destroyer of life and happiness—the dreaded malnutrition.

Abstinence under compulsion of circumstances is fortunately a rare thing. It belongs in the sphere of accidents, and the suffering it produces is as much due to panic as to hunger. Where the abstinence is self-imposed by voluntary choice, and there is nothing in the way of interrupting the fast, the presence of hunger pain is generally denied by the faster. Were the sensation of hunger in inanition completely dulled it would be difficult to account for the fact that starved animals resume feeding at the first opportunity. We should also fail to comprehend the compelling force of the hunger urge which has been the great factor in all migrations, both human and animal. The question naturally obtrudes itself as to whether or not the sensation of hunger persists during inanition. Clearly one must

differentiate between hunger and appetite. One is a primitive sensation common to all living organisms, the other doubtless an acquisition depending on the degree of mental development. It seems improbable that civilized man really knows the sensation of hunger. He takes his food in conformity with an established custom at stated intervals and irrespective of his actual needs. His whole existence is a cultivation of habits, and the change of habit is always apt at first to cause discomfort and a feeling of want. Irish or Bavarian peasants accustomed to their bulky diet of potatoes and bread suffer greatly when they are given a small quantity of highly nourishing food. Likewise persons who have habitually underfed themselves are much discomforted when they are put on a sufficient diet. Appetite and subjective feeling are evidently unreliable guides in the matter of nutrition.

Hunger, on the contrary, is an instinctive demand for nourishment akin to the sex craving. The former is concerned with the preservation of the individual, the other, with the preservation of the race. Hunger is a powerful urge common to all organisms irrespective of their degree of evolution. It is probably as strong in the protozoon as in the rapacious beasts of prey.

The mechanism of the hunger sensation in higher animals has been elucidated by the brilliant researches of Cannon and of Carlson. The sensation of hunger and the subsidiary symptoms —epigastric pain, faintness, nausea—are associated with periodic tonic contractions of the empty stomach. The objective method of recording these gastric contractions reveals that the rhythmic tonic spasms generally associated with the painful hunger pangs continue unabated, or may even become accentuated, during inanition. This important fact has been disclosed by Carlson's collaborators in experiments with dogs, rabbits, frogs and turtles. Carlson himself demonstrated the persistence of strong tonic contractions reverberating through the conscious processes of a human subject who fasted fifteen days, and in his own person in a fast of shorter duration. It is nevertheless a fact not to be disregarded that whenever fasting has been practised for therapeutic purposes and in the case of the professional fasters, the hunger pain and discomfort disappeared after the first several days of inanition. It is difficult to reconcile the lack of desire for food and hunger with the persistence of the hunger contractions. In the diseased organism this may perhaps be ac-

counted for on the assumption that the hunger contractions are inhibited through the bad taste in the mouth. In a number of diseases the absence of contractions has been experimentally demonstrated. The author's own experience has been that he can endure a brief fast of a few days without the least discomfort when not feeling well, but when in a normal condition the reaction has been extremely painful. It is indeed very doubtful whether a healthy individual, with a vigorous demand for nourishment, would willingly endure the hunger sensation unless he was dominated by some powerful emotion. The bravado of the professional faster, the autosuggestion or fixed idea of the protagonist and neophyte of the faith of the all-curing potency of inanition, the sublime egotism of the martyr, may all prove effective in actually inhibiting or at any rate masking the hunger pain. Strong emotions, anger, fear, worry, excitement, have a depressing influence on hunger sensations. An over-refined æstheticism of appetite may also act as a deterrent to the instinctive craving for food. One should not forget that inanition may result from just such emotional conditions. On the other hand, exasperated hunger sensations will completely dominate the conscious processes. Spurred by hunger, animals become daring and aggressive and forget fear. Human beings likewise quickly unlearn the gentle arts of social intercourse under the urge of the hunger whip. They grow cantankerous, egotistical and brutal.

We know of no factor more potent in completely repressing the hunger urge than the sex emotion. It is a familiar fact, of course, that children at puberty lose their appetite for food. Love and passion in full bloom may also occasion protracted undernourishment. Niclot, in an interesting discourse on the expression of love in ancient literature, refers to the type described by them as "consumptive love." The victim of the passion was thought to be under some supernatural spell. According to Theocritus the physical consequences of this consumptive passion are often very profound. The person fasts for days, and, if his passion meets with an insuperable obstacle, will be reduced to skin and bones. He becomes the victim of emaciation, progressive breaking down of force, insomnia, photophobia, of an instability of purpose and desire resulting from a disintegration of his will power.

A most striking instance of prolonged suppression of hunger

in mammals under the compelling force of the sexual impulse is recorded by Parker. The Alaskan fur-seal bull neither eats nor drinks for about three months in the year, during the entire breeding season. This is the more remarkable because at all times they are within easy reach of food. Living in a state of great excitement, fighting off intruders, chasing mischievous "bachelors," keeping jealous guard over his "harem" of cows, the sexually hyperactive bull experiences complete inanition. Parker relates that "by the middle of June the great majority of the full-grown bulls have established themselves on the beaches to await the coming of the cows. At this stage the bulls are in marvellous form. Their pelts are heavy and firm and their bodies in prime condition. In weight they are not far from 400 pounds. They seem to be possessed of inexhaustible energy. . . . Many of the bulls have been on the beaches from May and during that period between the time of their arrival and the end of July or early part of August, they touch no food. This fast of well over two months coupled with their incessant activity drains them of all their stored energy. Their fat disappears and they are reduced almost to skin and bones."

Acute inanition as a voluntary act is practised either by professionals as a feat of endurance, or by crank reformers who see in inanition a panacea for all ills of the flesh. Laboratory experience with fasters as well as long fasting among followers of certain religious sects prove that no harm can befall the healthy individual who abstains from food. The vigorous individual has a thoroughly healthy disregard for all problems of nutrition and is not likely to indulge in fasting as a pastime. Indiscriminate fasting, however, of patients whose strength is already impaired should be discouraged. In the hands of the skillful practitioner of medicine total abstinence from food may prove a wonderfully effective weapon in restoring health. The therapeutic value of inanition, however, should be studied experimentally and not be left to the judgment of amateur enthusiasts. The practical value of inanition will never be fully utilized until both laymen and the medical profession lose their instinctive fear of fasting. The experiences of recent years which through the medium of the press have reached a large audience will in course of time alleviate the entirely unjustifiable fear of abstention from food for longer periods.

The biological fact that under inanition it is the weakest

parts of an organism which are the first to undergo destruction and to be eliminated from the body may be safely put at the foundation of the therapy by this means. It is doubtless true that it is a rational therapy in affections of the alimentary canal. Through its tendency to lower the body temperature, inanition would be especially valuable in inflammatory involvements of the gastro-intestinal tract as in typhoid fever or diarrhea. Guelpa was among the first to appreciate the importance of inanition in the relief of diabetes. The system, now scientifically established by Allen, is generally recognized as an effective method in combating this disease.

Since emaciation frees the organism of the excesses of inert material in its tissues it is often a great boon. The study of physiological inanition should dissipate all terror of a possibility of endangering existence. Laboratory as well as clinical experience corroborates the rejuvenating effect of inanition. If not too prolonged inanition is distinctly beneficent and may be useful in overcoming somnolence and lassitude as well as in improving the fundamental organic functions (circulation, respiration), muscular strength, or the acuity of the senses. To understand this beneficent influence we may imagine the organism as a wayfarer starting on a long journey provided with a big supply of victuals. Crouching under his heavy load he trudges along slowly and with difficulty. His heart is overworked, his respiration is forced, and every obstacle in the road quickly wears him out. Gradually his supply of victuals is consumed and as the burden becomes smaller, his step grows lighter. He advances more quickly and overcomes obstacles more easily because his muscles are less fatigued. The organism's efficiency improves in a similar manner when the excessive load of inert material in its tissues is used up. The training of athletes bent upon creating a high degree of strength and endurance is likewise concerned with a reduction of the inert fat deposits and a simultaneous building up of the muscle mass. The salmon furnishes us another interesting example. At the time they commence to migrate from the sea towards the streams their muscles are thoroughly encumbered with huge masses of fat. Fasting all during their long journey, which lasts many weeks and months, they are in a much emaciated condition when they get to the upper reaches of the rivers where the currents are rough and swift. Freed from the fat, however, their muscles are now agile

and nimble, and it is at this time that the salmon display marvellous endurance and skill, admired by all sportsmen, in progressing steadily against all the odds of the tumultuous current, water falls and obstructions.

Except where it occurs in nature, acute inanition is primarily an individual experience. Therapeutically it will remain relatively unimportant until education overcomes the innate fear and distrust of the method, and from a sociological standpoint it is practically of no significance. Where it affects large masses, however, inanition is a corollary of certain evils deep-rooted in the social organization; it is an unwelcome and perpetual visitor in the homes of the lowly, and is not the beneficent agent of which we spoke. Here it appears as the insidious malnutrition which silently saps and undermines the health of the mass. It does not signalize its presence by engendering a violent urge for food; it just corrodes the powers of resistance remaining unnoticed often until the wreck it causes is hard to redeem. It does not kindle the latent hunger instinct to defy fear and hazards; it blights ambition and gnaws away the fine threads of social ties by generating an irritable, unamiable, cantankerous disposition.

Frequently malnutrition results from nothing else than ignorance. The lack of comprehension that the law of conservation of energy applies to the functioning of the living organism is doubtless responsible for the fact that some deluded folk either reduce their consumption below actual needs of their body, or else consume stuffs entirely inadequate from a physiological standpoint. Generally under such circumstances their vitality is nibbled away by slow starvation. Insufficient consumption of nourishment gradually becomes a vicious habit. The dulled state of the psychic mechanism of appetite and the discomfort actually experienced from taking larger quantities of food are mistaken for the true sign of the organism's demands. The enfeebled appetite misguides the undernourished person to scrimp still more in his diet. The physical consequences of this malnutrition are great depression of bodily activity, general disinclination to exertion, easy fatigability, as well as anemia and poor circulation, neuritis and various neuroses. It is also a well recognized fact that the undernourished individual craves every kind of stimulant, a matter which gains considerable importance when the malnutrition extends to large groups of the population.

One can derive much hopefulness from the fact that the effects of malnutrition, if early recognized and combated, are evanescent. With proper care and abundant nourishment the organism can be built up again, as will be discussed in one of the later chapters. In his official report on "Food Conditions in Germany" Professor Starling ascribes the collapse of national resistance to the circumstance that the urban population (more particularly, the working people) was starved, and this generated widespread apathy, listlessness and hopelessness. He expresses the opinion that this population of Germany would have to be nursed back to health just like a sick patient and that at least "one or possibly two generations must pass before Germany can recover her former efficiency."

A new and serious source of malnutrition has arisen in our modern industrialized civilization. By the implacable economic forces women have been drawn away from their traditional place in the home into the turmoil of industrial production. At the same time the factory has intruded itself into the home and has preempted much of the woman's function of preparing the family's food. The manufacture of foods dispensed in cans and all ready to be served has insinuated itself into the homes of the people to such an extent that it has become literally true that many households can now-a-days be conducted with the aid of two implements—the cork screw and the can opener. The evil of these industrial conditions is seen not only in the circumstance that the younger generation is deprived of proper maternal care, but also in the fact that owing to qualitative deficiencies, tinned goods, when these are the staple article of diet, may produce the effects of partial inanition. A better understanding of the fundamental principles of nutrition would perhaps offset this danger to the health of the population.

However, ignorance of the essentials of the physiology of nutrition is not the only nor the gravest peril. This can more or less be overcome effectively by disseminating information. Unfortunately, the great peril of malnutrition is rooted deeper, in poverty coupled with ignorance, and against this conspiracy the spread of the gospel of nutritional science can accomplish little. Furthermore, as a social phenomenon malnutrition is not simply a matter of either insufficient or improper nourishment; it is the sinister combination of blighting influences of poverty—over-crowding, under-clothing, unhealthy and unhygienic envi-

ronment. Here is the fertile soil on which tuberculosis reaps its ghastly harvest.

Visiting Germany immediately after the collapse in the late war, Harris was impressed with the blessings in disguise which the few lean years have brought to the people. He found that there was a striking decrease in the number of patients suffering from chronic nephritis, chronic ailments of the stomach and liver, from Bright's disease and diabetes. He was generally informed by practitioners that they "did not have gout any more in Germany." Had Harris looked at the matter from the perspective of the sociologist, he would have noted that frugality benefited a class of people with whom eating was generally a social grace if not a central interest in life. The diseases mentioned are proverbially the price paid for the social privilege of over-eating. As for gout—a well recognized rich man's disease—this has always been a badge of class distinction. The reduction of the diet of this chronically overfed population to the limits of a healthy and normal basis has very evidently been a benefit. But in the lower strata of society where the population lives in the precarious region of the minimum requirements, the increased stinting in nutrition manifested itself quickly in an appalling spread of malignant tuberculosis, especially among children, in an increased death rate and general physical degradation. It is of this working population of Germany that Professor Starling says that it would have to be nursed back to health and physical efficiency.

A striking example of wretched physique resulting from the wretchedness of living conditions is presented by the Jews of Poland. Their physical strength, their muscular power has diminished in each succeeding generation; their blood is poor, their stature is small, shoulders and chest narrow. Many have an emaciated pallid look, and show signs even of racial decline and degeneracy. Held back by various disabilities, crowded in the Jewries of Poland, with limited opportunities for gaining a livelihood, they have literally been the victims of malnutrition for generations. Their poor constitution, physical frailty and stunted growth make them manifestly unfit for heavy work. Leroy-Beaulieu says of them, "Few races have so many men who are misshapen and deformed, disabled or hunchbacked, so many who are blind, deaf-mutes, or congenital idiots." Close inbreeding owing to marriages between near relatives can hardly

be held responsible for this physical degeneracy. The inbreeding only accentuates the evils of age-long confinement, lack of exercise, lack of pure air, lack of healthy social environment and above all else, lack of wholesome nutriment. The rôle played by malnutrition in producing racial deterioration of the mass of Jews especially in the Polish ghettoes can be best appreciated from the fact that investigation of their living conditions has shown that they were so poor that for generations they subsisted upon nourishment below the actual minimum requirements. Tchubinski actually found that the Jews of Little Russia and Poland consumed less food than either their Greek Christian or Polish Catholic neighbors. Transferred to a less forbidding environment, the inherent recuperative powers of the organism under favorable nutritive conditions show remarkable effects already in the first or second generation.

The influence of religious fasting upon the health of the population is little realized. The complete inanition practised by individual devotees or even by whole ascetic sects is of no concern in this connection. From the point of view of physical deterioration it is the malnutrition associated with religious custom that should be mentioned. Even in this respect the effect is different in different classes of society. In the Middle Ages it seems that the rich could forego fasting and obtain absolution for a price. Mass starvation from religious devotion is an important phenomenon in Greek Catholic countries. Considering that three days in the week are fast days besides several protracted fasts at various seasons it is safe to say that fasting is prescribed for about one-half of each year. The fasts might be a benefit if they limited only the consumption of meat. In the Greek Catholic Church, however, the prohibition extends also to eggs and dairy products. As usual the poor population is especially the sufferer under these restrictions. The young children in particular are the victims. Medvedjev found that the boys and girls of school age all show a loss of weight and stature during the fast seasons. The malnutrition of the mass of the people is so great that women are unable to nurse their babies, and there is usually an enormous mortality among the infants. Scurvy and pellagra, eye-diseases (night-blindness) and typhoid are common incidents of the fasting population. Alcohol is consumed in unusual quantities by the poor people to

still the constant irritation which marks their malnutrition. The peasantry deadened itself with drink.

Famine is the most acute form of malnutrition. It is truly one of the cruelest scourges of mankind. It would be impossible to estimate the extent of damage it does in terms of physical suffering and ruin. Those who fall by the wayside are soon enough forgotten, but famine leaves a trail of human derelicts, of cripples, of blind and feeble, of a generation with undeveloped sinews and brain. The fundamental cause of famine is in all cases probably economic, but crop failure is the immediate cause of the situation when millions of people are without means of subsistence. Those who write about famine vary in their opinion as to whether this is punishment meted out by an unpropitious God or should be laid squarely at the door of ignorance and oppression, greed and exploitation. In certain countries famine is practically an endemic occurrence. And strangely enough the classical lands of famine are also under foreign dominion, like Ireland and India, or under a tyrannical exploitation as Russia was in the time of the Czars. In India famine played a more momentous and at the same time more tragic part than either war or pestilence. It spread at times over many thousands of square miles, affecting at once millions of people. Since its domination by the East India Co. and in the subsequent fifty years under the Crown, India suffered twenty-two great famines and a number of less extensive scarcities. In the great famine of 1876 alone about five and a half million persons died in excess of the usual death toll, though of course it would be altogether impossible to discriminate how many deaths were directly due to starvation and how many to various diseases brought on by severe malnutrition.

Famine is not merely destructive of health and physique, it is in a still greater degree a disrupter of morale and character. In the sharp struggle to maintain life all scruples are overcome, neighbor is against neighbor, and the strong are ruthless towards the weak. With wonderful force of simplicity does a thirteenth century Russian chronicle relate the horrors of the famine in the Novgorod province: "We were all in a fury of irritation; a brother rose against his brother, a father had no pity for his son, mothers had no mercy for their daughters; one denied his neighbor a crumb of bread. There was no charity

left among us, only sadness, gloom, and mourning dwelt constantly within and without our habitations. It was a bitter sight, indeed, to watch the crying children, begging in vain for bread, and falling dead like flies."

Still more appalling, however, is the aftermath of famine. Little actual information can be gathered of the after-effects. Prugavin tells of the many thousands of peasants afflicted with scurvy, typhus, spotted fever, influenza and diarrhea in the terrible famine which spread over the central provinces of Russia in 1898. Even long after the famine nearly all children suffered from various skin eruptions, rickets, diarrhea and purulent inflammation of the eyes. The doctors who went into the pestilential districts to offer succor to the famine victims have noted the unusually large number of people with severe diseases of the eyes. The great Irish famine of 1848 likewise left a trail of blind men and women in its wake. Dr. Emmet reports that the number of blind increased from 13,812 in 1849 to 45,947 in 1851. We will learn in our subsequent chapter on partial inanition that this is a specific effect of certain kinds of inanition, and is invariably met with in every instance of malnutrition.

PART II

PHYSIOLOGICAL INANITION

CHAPTER I

HIBERNATION

a. Hibernation and Allied Phenomena

In the cold season, while a frozen silence prevails in nature, many organisms fall into a state of immobility and lowered vitality only bordering upon a state of potential life. This period of their existence is commonly called hibernation. By an unknown mechanism of adaptation the life of various animals follows the phases of the sun, the primordial source of energy on earth. With the approach of winter, when the rivers are congealed in their sinuous course and the earth is hidden beneath a mantle of snow, a number of animals which would not survive exposure to the severe environmental conditions retire to special places of concealment, where singly or in groups they remain in a more or less uninterrupted state of suspended animation. When the Springtime sun awakens spell-bound nature, the hibernating animals emerge again from their prolonged lethargic state.

During this period of hibernation, lasting in some cases several months, the animals subsist entirely at the expense of their body reserves, and draw upon fat as well as protein and carbohydrate for their metabolism. The materials in their tissues furnish the minimum amount of energy which is indispensable to keep life flickering until more favorable conditions of existence arrive. Small mammals, notably some of the rodents, insectivora and cheiroptera, pass intermittently through such a stage of physiological inanition. The most significant phenomenon accompanying this form of physiological inanition is the lowering of the body temperature practically to the level of that of the environment. In this respect the hibernating mammal behaves exactly like the cold-blooded animal which spends the winter season in a state of torpor.

The ability of the hibernating organism to withstand lowering

of the internal temperature to just a few degrees above zero is undoubtedly the saving factor in the situation. It is well known that extreme cold is not injurious to living substance. The revival of frost caterpillars is a familiar occurrence, and in recent years Carrel has shown in a series of brilliant researches that segments of arteries may be successfully grafted after years of refrigeration. The piece grafted upon another organism resumes its normal function after its vital activities have been suspended for several years. The refrigeration and the subsequent revival are essentially an artificially produced hibernation.

We shall discuss later the profound changes produced in the entire organization of hibernating animals. The origin of hibernation is beyond our ken, but various allied phenomena can throw light upon its nature. The experience with refrigerated tissues is very significant in this respect. It may likewise be recalled that frogs have occasionally survived imprisonment in solid blocks of rock, a matter which has been investigated in the laboratory by Richet.

The manner in which Russian peasants have occasionally weathered the winter in the trying years of famine, demonstrating a keen ingenuity in coping with elemental hardships which beset mankind, reveals at the same time the remarkable resourcefulness of the organism in meeting emergencies. Massed closely together, on the top of a wide stove, entire families of peasants, deprived practically of every means of subsistence, spend the dreary winter season in an almost uninterrupted sleep, known in the famine visited districts by the name of "liojka." Well protected against loss of heat by close contact as well as by their fur coats, members of the entire household and frequently of entire villages remained, with occasional interruptions, in a state of winter sleep, preserving their energy by limiting its dissipation. Of course, this "winter sleep" bears only a superficial resemblance to the hibernation of animals.

Drought is likewise an environmental condition under which life remains potential. Seeds are classical examples of suspended vitality of this sort. In a dry state these potential plants may survive for years and withstand every hardship. Several groups of animals (rotifers, tardigrades and certain nematodes) survive accidental desiccation, or live through the dry season of the year in a state of suspended vitality, to resume their normal existence once more when returned to a moist medium.

Rotifers, whose normal life period is not more than a few weeks, are known to have been revived after several years of desiccation. In 1860 a select committee of the French Academy vouched for the possibility of revival after prolonged desiccation. In recent years Jacobs showed that rotifers of all ages, may recover after an extended period of desiccation which he found by means of chemical and physical tests to be absolutely complete.

It is still a matter of uncertainty whether in these instances of suspended animation physiological activity is at a standstill or is merely reduced to a minimum which our methods are too crude to detect. Tashiro's measurements of carbon dioxide produced by seeds are very important as indicating that a feeble oxidative process goes on continuously.

There are several reports of Indian fakirs who have practised suspended animation. These are generally regarded with much skepticism because of circumstances that seem entirely incredible to the human imagination. But allowing for impositions undoubtedly perpetrated on various occasions upon credulous audiences, it is nevertheless fairly certain that some of the feats of suspended animation performed by fakirs may be considered genuine. A survey of the phenomena of suspended animation in nature leaves little doubt that there is nothing supernatural in its exercise by a human being. There are no scientific records of such feats by fakirs and with the elementary facts unknown little can be surmised regarding the physiological process. But some benefit may be derived even from the lay reports.

Probably one of the most authentic accounts is that of an Amritsar fakir who had been interred for forty days and afterwards exhumed and revived. This fakir called upon Runjit Singh offering himself to be buried alive for forty days. Runjit accepted the offer and had a special tomb erected on his estate. Prior to the burial the fakir had undergone a very severe training for twenty days, during which period, while under strict surveillance, he drank only milk and took excessive amounts of purgatives. At the appointed day the fakir appeared before a gathering of distinguished guests. After certain preparatory acts he performed a series of very deep inspirations whereupon he fell to the ground and remained motionless. He was put in a strong coffin and buried in a grave in the specially erected mausoleum. The heavy door of the sepulchre was locked by Runjit Singh's most confidential agent, and from then on the

condition of the grave was regularly inspected under Runjit's personal supervision. When at the end of forty days the coffin was excavated and the lid removed the fakir seemed none the worse for his experience though somewhat paler. He was immediately attended by a servant whom he had instructed for the occasion. In the evening of the same day the fakir was present at the reception given in his honor by the singh.

Unfortunately no scientific data exist of such simple observations even as the body temperature, pulse or rate of respiration which could throw light on this truly remarkable experiment. A few of the general observations, however, made by eye-witnesses of this performance of the Amritsar fakir allow us to draw some interesting analogies. It had been noticed by those present, when the fakir was exhumed, that there was a difference between the temperature of the head and the rest of the body. The general statement that the head was unusually hot must be interpreted to mean that the difference between its temperature and that of the trunk was very appreciable.

It will be subsequently shown that the difference in temperature of the anterior and posterior portion of the body is a universal phenomenon in hibernation.

The resuscitation of the fakir has also many points of resemblance to the natural awakening of hibernating animals. The first thing the servant did in the effort to restore his master to life was to apply two halves of a freshly baked bread to the fakir's head. The object of this was obviously to quickly raise the temperature of the brain, and to invigorate the cerebral circulation. The next step in the process, the massage of the stiff limbs, likewise had for its purpose the stimulation of the peripheral circulation. The awakening of hibernating animals is inaugurated by the rush of blood to the brain, the temperature of the head rising rapidly to the normal level, while the rest of the body still remains cold. The further warming of the organism is facilitated by vigorous twitchings and convulsive movements of the limbs which invariably occur in the course of awakening from hibernation.

In one respect the mystery of the fakir seems to have found a scientific explanation, namely, with regard to the inhibition of the heart.[1] This is generally brought about by the irritation

[1] "Das Kunststück der indischen Hexenmeister, die Herzkontraction willkürlich zu verlangsamen, ist jetzt gelöst, nachdem Donders gezeigt hat, dass

of the fibers of the *Accessorius Willisii* which run in the vagus. The *N. accessorius* supplies also muscles of the throat and an irritation of the proper muscle, as was recently demonstrated, can indirectly cause the heart to slow down or even cease entirely its activity. The "deep breathing" of the fakir may possibly have purported the inhibition of the heart action by contracting the particular set of muscles in the throat.

By whichever trick the fakir succeeded in suspending his vital activities, it is highly probable that what he accomplished is neither supernatural nor mysterious, but a clever imitation of nature's own work.

b. Changes in Body Weight During Hibernation

Nearly every student of the hibernation problem has been confronted with two problems of fundamental importance: first, the rate of loss of body weight in the course of hibernation; and, secondly, the cause of the transitory rise in weight which has been frequently observed. This last phenomenon is the more singular since the animals are in a state of continuous inanition during hibernation.

The first extensive research on this subject was made by Valentin, some of whose results with hibernating marmots are given below:

Marmot	*Initial Wt. (Grams)*	*Days of Hibernation*	*Loss in Weight*		
			Grams		*Per Cent*
			Total	*Per Day*	
1.	3274.0	40	638.5	15.96	19.5
2.	1083.1	40	89.5	2.24	8.3
3.	944.4	70	211.2	3.02	22.4
4.	1322.0	134	242.5	1.81	18.3
5.	1235.2	134	287.9	2.15	23.3
6.	669.3	146	229.3	1.57	34.3
7.	1006.5	169	409.5	2.42	40.6

durch willkürliche Kontractionen der vom Accessorius versorgten Holzmuskeln das Herz zum Stillstand bringen kann, indem mit der Reizung jener Muskelaeste des Nerven auch gleichzeitig seine Herzaeste angeregt werden. Dieselbe Wirkung kann oder auch durch Reizung von Sympathicus fasern in der Bauchhöle zu Stande gebracht werden, denn auch bei einer solchen kann das Herz in der Diastole stillstehen, gerade so wie bei der directen Reizung des Vagus." (Ziemssen, *Cyclopædia of Medical Practice*, Leaming, Vol. 6, p. 275.)

The last two animals which suffered the largest loss—over one-third of the initial body weight—hibernated also the longest time. These animals were frequently awake and this, of course, is responsible for the very large loss sustained. Leaving therefore these two marmots out of consideration, the total loss in body weight during 40 to 134 days of hibernation is about 8 to 23 per cent. According to Mangili the loss occasioned by a three months' hibernation is only 12 to 14 per cent of the initial weight.

The relatively small proportion of body weight lost in hibernation gains particular significance when compared to the loss sustained by the same organism when subjected to experimental inanition. Hári finds that hibernating bats lose only 0.08 per cent of their initial weight per day, while during an experimental fast they lose daily 2.6 to 3.3 per cent at 19° C. and 29° C. respectively. The slow rate of diminution of hibernating animals is similar to that observed in the case of starving reptiles or amphibians, and in either case is doubtless the result of a slow rate of combustion in the organism.

Polimanti from his studies of hibernating marmots draws a general inference that the loss of body substance is inversely proportional to the animal's initial weight. Maurel et Rey-Pailhade have demonstrated this rule even more convincingly on hibernating turtles.

Maurel furthermore shows that the outside temperature has a direct influence upon the rate of loss in body weight. According to his observations an increase in temperature by 3.1° C. (11.5° to 14.6° C.) resulted in a change of the daily loss from 0.38 to 0.81 grams per kgrm. In another instance a rise of temperature by 3.2° C. (10.3° to 13.5° C.) was accompanied by a change in the daily loss from 0.32 to 0.62 grams per kgrm. In other words, the rate of loss has been practically doubled by a rise in temperature of a little over 3° C.

Dubois thinks that the greater loss of weight at the higher temperature is due to the fact that the continuity of the hibernation is more frequently interrupted.

Searching for the fundamental laws which govern the loss of body weight in hibernation, Polimanti formulates the hypothesis that the curve of the loss represents a section of a rectangular hyperbola. As will be shown later, Luciani had already attempted to describe the curve of loss sustained by a fasting organism in

terms of a hyperbola, the changes in body weight obeying a definite mathematical rule. Polimanti concluded that the proportional loss in weight diminishes gradually as the hibernation advances, the losses suffered during equal periods of time being proportional to the square of the body weight at the beginning of each period.

A close examination of Valentin's curves as well as those of Bellion shows that they approach more nearly a straight line with a constant slope. Considering the inherent difficulty of getting reliable results on the weight of hibernating animals, owing to the ease with which their sleep is disturbed, and the paucity of Polimanti's data there seems little warrant for his broad generalization. Anticipating what is reserved for a fuller discussion in a further section, there is no justification either for the assumption that the curve of loss in body weight during inanition follows the course of a hyperbola.

Barkow, I believe, was the first to observe that although the hibernating animal takes no nourishment, its weight does not diminish continuously but occasionally remains constant or even shows a slight gain. This singular phenomenon naturally attracted much attention and led to a number of more or less plausible conjectures. Recently Nagai questioned the validity of the earlier observations showing temporary gains in body weight. His own data, however, are scarcely enough to discredit the numerous observations recorded by other investigators.

In the case of one marmot Valentin found that of the 98 weighings made 64 showed a decline and 19 an increase in weight, while 15 determinations showed neither gain nor loss. Polimanti made a similar observation on his three hibernating marmots, as shown in the table:

Marmot	*Changes in Body Weight*		
	Increased	*Stationary*	*Decreased*
1.	15	15	71
2.	9	16	74
3.	12	4	59

Dubois registered these slight temporary rises in body weight with the aid of a Rédier automatic compensating balance, thus corroborating their occurrence.

Various factors were held responsible for this unique fact.

The earliest hypotheses attempted to explain these positive variations as being due to the hygroscopic properties of the animal's fur. But, as Polimanti has shown, variations in the body weight of his marmots appeared even when he kept them under different conditions of humidity. Nagai experimenting with dormice found that the daily losses increased roughly in the ratio of 1 : 4 : 6 as the degree of humidity of the surrounding medium diminished, and at no time did he find a gain in weight. His experiments are not very conclusive, however, since the animals were maintained in a current of dry air which probably favored evaporation. The increases in weight being generally slight in extent, it is not improbable that an excessive loss of moisture from the animal offset any positive variation in the body weight which may have occurred.

There is good evidence for believing that there is an optimum temperature at which positive variations in weight appear most frequent. Since this temperature is also most favorable to tranquil and deep sleep, the temperature probably plays the part of an auxiliary factor. Of course, there is no reason for assuming with Polimanti that the oscillations in body weight are somehow regulated by cosmic conditions, a low barometric pressure presumably tending to induce an increase in weight.

The increase in weight which almost invariably takes place while the animals are firmly asleep must depend upon some intrinsic factors. It has been suggested that it is occasioned by a retention of either oxygen or carbon dioxide in the body, while some maintain that it is due to a transformation of fat into glycogen as a result of incomplete oxidation. This hypothesis has been severely criticized by Nagai, but it is not at all incredible that during profound sleep, while the vitality of the organism is at the lowest ebb, intermediary products of oxidation may be formed which are not readily eliminated from the system. The increase in weight is generally followed by an abrupt loss which is the greater the larger the preceding gain. This must apparently result from a rapid and augmented excretion as soon as the intermediary substances are oxidized to water and carbon dioxide.

c. Changes in Weight and Composition of Organs

We reviewed the facts pertaining to the total loss in body weight, which probably never exceeds 20–25 per cent of the

animal's initial weight. The object now is to show to what extent the various parts of the organism participate in this loss and how their composition is affected by these changes.

Valentin and his pupils gave much attention to these problems. The former made numerous determinations on the weight of different organs of marmots killed at various stages of the hibernation. It is evident from the subjoined table that the fat deposits are drawn upon most freely to satisfy the needs of the organism in hibernation.

Organ	*Per Cent of Total Loss Sustained*	
	44 Days of Hibernation	*163 Days of Hibernation*
Fat	3.19%	16.28%
Musculature	...	7.63
Skeleton	1.79	1.95
Skin	0.46	5.57
Hibernating Gland	0.35	0.88
Stomach	0.27	0.86
Liver	0.24	1.88
Respiratory Organs	0.04	0.44
Salivary Glands	0.02	0.02
Adrenal Bodies	0.018	0.02
Urinary Bladder	0.009	...
Spleen	...	0.01
Heart	...	0.16
Brain	0.07	...
Spinal Cord	0.01	...

After 44 days of hibernation 3.2 per cent of the total substance lost is fat, the total loss being only 8.3 per cent of the initial weight; after 163 days, when the total loss was 35.1 per cent, 16.3 per cent of the loss was at the expense of fat. In other words, nearly one-half of the organism's expenditure came from the fat depôt. Of the other organs which share in an appreciable manner the total loss sustained by the body we may mention the muscles, skeleton and the skin, while the lungs, heart, brain and various glands contribute but sparingly to the support of the organism during hibernation. At the end of 163 days of hibernation one-fifth of the entire loss is derived from the muscle tissue, one-seventh from the skin, one-eighteenth from the skeleton, etc.

The table which follows gives a still clearer picture of the participation of the several organs. Already at an early stage

in the hibernation 20 per cent of the fat is consumed, and at the end of 163 days it is all but exhausted. The hibernating gland containing a very large proportion of fat loses over two-thirds of its mass, while the liver and stomach lose about one-half. It is especially noteworthy that the musculature diminished by less than one-third of its original mass. This fact will gain significance when the reduction of the musculature in experimental starvation is considered.

Relative Loss of Weight Sustained by Different Organs

Organ	*44 Days of Hibernation*	*163 Days of Hibernation*
Fat	19.15%	99.31%
Muscles	....	30.30
Skeleton	....	11.69
Skin	....	35.31
Hibernating Gland	27.15	68.78
Stomach	14.57	47.05
Liver	7.57	58.74
Respiratory Organs	4.14	44.56
Salivary Glands	13.13	15.00
Adrenal Bodies	39.13	45.65
Spleen	9.78	10.87
Heart	....	27.48
Brain	7.07	....
Spinal Cord	4.76	....

Considering the extent to which each of the several parts of the organism are affected in hibernation, it is not surprising to find marked changes also in composition. Aeby found that marmots lose much water throughout hibernation (eliminated as urine and through evaporation from lungs and skin); as a result of this the muscles and blood become dehydrated and the water content diminishes; in the brain and spleen, on the contrary, the water content remains unchanged.

Both the musculature and the blood lose relatively much of their mineral constituents, while in the brain, spleen and liver mineral substances accumulate considerably. There is, therefore, a mere shifting of the mineral substance from one part of the organism to another. Aeby did not seemingly appreciate that the accumulation of the inorganic material in the spleen and liver coinciding with its withdrawal from the blood may be the outcome of a progressive disintegration of the red cells. Yet, as can be inferred from Quincke's investigation, the accumu-

lation is very likely due to a liberation of iron from the erythrocytes. Quincke found that the blood of a hibernating marmot contains only 64 per cent of the normal hemoglobin quantity and 70 per cent of the normal number of blood cells. He also discovered the presence of iron in the spleen, marrow cells and in the capillaries of the liver. This iron he considers to be derived from destroyed red cells and is probably utilized afterwards in the regeneration of the blood.

Valentin, Claude Bernard, Aeby and others have shown that along with the consumption of the various body constituents there is likewise a new formation and storing of glycogen in the liver. It is commonly believed that upon awaking the animal rapidly katabolizes the accumulated glycogen. The following record given by Dubois is quite to the point in this connection:

GLYCOGEN IN 1000 GRAMS OF LIVER (MARMOT)

Days of Hibern.	*Animal Asleep*	*Animal Awaking*
4	6.05 g.	0.2 g.
7	8.88	0.0
9	8.65	trace
10	16.32	0.0

Weinland and Riehl who studied this question more recently come to the conclusion that the absolute quantity of glycogen remains constant from December till March, the per cent of the glycogen increasing as the body weight diminishes. Furthermore, they maintain that the glycogen accumulates in the muscles, while the liver and the other organs are more or less depleted of their glycogen. The awaking process is accompanied by striking changes in glycogen content.

	Weight of Marmot	*Glycogen*	*Glycogen per Kgm.*	*Remarks*
Before Awaking	2520.7 g.	9.03 g.	3.58 g.	computed
After Awaking	2515.7	4.775	1.89	found
Difference	—5.0	—4.255	—1.69	

Thus the total quantity of glycogen of the body diminishes to nearly one-half its original mass in the few hours of the awaking, the largest loss being borne by the liver.

Marguerite Bellion, too, finds that in the case of hibernating snails (Helix) glycogen accumulates, the maximum content being generally observed at the beginning of the hibernation. She found, furthermore, that glucose was present in the liver and several other organs, the quantity reaching a maximum about the end of hibernation. Immediately upon resuming normal activities the glucose almost completely disappears from the body.

Bellion also observed a considerable dehydration of the muscular and hepatic tissue and an accumulation of lecithin.

A thorough survey of the chemical changes in the composition on hibernating glands of the hedgehog have been made by Carlier and Evans. They found that the per cent of water varies from 40 to 60, and of the organic substances fat alone represents a considerable amount, ranging from 17 to 40 per cent of the gland. The fat is about nine-tenths olein, the remaining one-tenth consisting of stearin with traces of palmitin, lecithin and pigments. The olein is used up first during the hibernation, and this may be due to the fact that being an unsaturated body it lends itself more readily to oxidation.

Vignes found the "hibernating gland" (*masse hibernale*) to consist largely of a substance soluble in ether and chloroform but insoluble in acetone. It shows, therefore, the characteristics of a phosphatid which he identifies as jecorin.

Experimenting on mice and rats, he extirpated the organ which is homologous with the hibernating gland. These experiments, although few in number, are nevertheless very suggestive. Vignes finds that the gland is not only rich in lipase, but that its removal results in a marked diminution of the lipase in the serum of the operated animal. He also states that the substance of the gland has no amylolytic action but is strongly antitryptic. His experimental data are unfortunately meagre but, if correct, would make it seem probable that in the hibernating organism, where this organ is greatly developed and by a series of lobules extends widely through the organism, its main function is to preserve the proteins through its antitryptic activity.

It is a remarkable fact that in inanition incident to hibernation the muscular tissue is wasted much less than in experimental inanition. It would be interesting to prove that the "hibernating gland" is an organ which in the group of hibernating animals has assumed the highly specialized function of saving the valuable protein store of the organism from excessive de-

struction during the seasonal recurrence of stress and hardship. At the same time it not only serves as an important food depôt by reason of the great accumulation of fat in it, but, as Vignes' experiments on the lipolytic action of the *masse hibernale* of rats strongly suggest, it also promotes the utilization of fat substances from other sources.

d. Changes in Body Temperature

Every object possesses a certain amount of heat but the body temperature of living organisms is an acquisition which by a process of evolution has finally secured for them independence of their environment. Poikilothermic, or cold-blooded animals may be said in general to possess body heat, their inner temperature varying with the temperature of the exterior, especially if the medium is water. It is still an unsettled problem whether cold-blooded animals are as much at the mercy of the outside temperature influences as inorganic bodies, though the evidence points to the existence of a power of heat production, however feeble this may be. In the evolution of the homothermic, or warm-blooded animals two factors must be clearly distinguished with regard to their heat-regulating mechanism: the elaboration and perfection of the primitive method of heat production, and the development of the specialized mechanism for adjusting the dissipation of heat. Echidna, the lowest member in the scale of warm-blooded animals, is but an imperfect homothermic organism. It does not have a normal and constant temperature, which may even vary within 10° while the surrounding temperature varies from 5° to 25° C. These animals hibernate during the cold months, and at that time their body temperature is only a few fractions of a degree above that of the environment. Newly born mammals show likewise a defective heat regulating capacity which, however, improves in the course of their development and growth.

Leaving out of consideration the poikilothermic animals whose temperature varies directly with that of the environment and whose vitality is so deeply affected by the onset of the cold season as to become completely suspended as long as this lasts, our attention will be turned for the present chiefly to animals which occupy a place intermediate between cold-blooded and warm-blooded organisms. Recent investigations by Simpson on

woodchucks show that these animals do not possess what is generally regarded as a normal temperature. In the free state their body temperature ranges from 33.6° to 41.2° C. Horvarth observed that susliks (*Spermophilus*) frequently show widely different temperatures (as much as 15° C. apart) when they fall asleep in the winter, although they are under precisely similar conditions and even in close contact with each other. These facts support strongly the assumption that they are imperfect homothermic organisms. There is a close parallelism between the state of the hibernating organism and its inner temperature which is quite independent of the outside temperature. I select the following illustration of this point from a number of similar instances.

Condition of Hedgehog	*Rectal Temp.*	*Air Temp.*	*Difference*
Practically Awake ...	36.2° C.	4.1° C.	32.1° C.
Drowsy	14.5	2.8	11.7
Asleep	5.6	2.1	3.5

But while the animals are asleep their inner temperature corresponds to the temperature of the environment. Dubois observed that the rectal temperature of four marmots ranged from 4.6° to 4.8° C. while the outside temperature was 4° C.

The temperature of the animal is thus seen to be only a fraction of a degree above that of the air. Other observers (Barkow, Monti, etc.) claim that it may even fall below the temperature of the surroundings. Valentin, who likewise made such observations, is cautious not to ascribe to this any significance and thinks that it is simply due to the fact that the temperature at the bottom of the cage is cooler than at the top. Since the air is warmed more rapidly than the body it is even more probable that the occasionally observed fall of the temperature below that of the environmental results from the fact that the body temperature has been measured before the inner and outer temperatures had become equalized.

The temperature of the front and hind portion of the hibernating organism shows a very marked difference. Marés attributes this to a suppression of the circulation in the posterior portion of the body. Berger, who carefully examined this matter, found in the case of marmots an average œsophageal temperature of 15.28° C. and a rectal temperature of 14.15° C.

Valentin found that the difference between these two temperatures is on the average 1.03° C., while the animals are quietly and deeply asleep. The difference becomes much more pronounced when the marmots awaken, the head and chest warming up much quicker than the hind portion of the body. This gave rise to the belief that during the process of awaking the seat of the heat generation is in the liver, and from there it spreads to the thoracic muscles affecting ultimately the entire organism.

Hibernating animals at no time behave like genuine homothermic organisms, but neither do they reveal purely poikilothermic tendencies. It is even doubtful,—and most physiologists concur in this opinion,—that the cold weather is the direct cause of the hibernation. Simpson showed by means of automatic records that the average temperature in holes inhabited by woodchucks is lowest in March and April, i.e., at the time when the animals emerge from the hibernating state and become again active.

The animals usually fall asleep when the outside temperature is about 15° C., and as the temperature drops to 10° C. their sleep is already profound. Although the inner temperature follows closely the temperature variations of the outside medium even to a much lower level, the animals resist vigorously cooling beyond zero, and, indeed, before the temperature reaches such a low point they wake up and by active movements try to prevent the further lowering of their body temperature. Bats, for instance, awake and fly about briskly until their temperature becomes normal. If the grip of the cold wave relaxes in the meantime the animals save themselves; otherwise, their body cools off again and they freeze to death.

In the discussions of the changes in body temperature great interest is attached to the rising of the temperature during the process of waking. In the brief span of time occupied by the awaking an enormous development of heat takes place which is unparalleled in living beings under any other circumstances. Indeed, within a few minutes the temperature may increase by several degrees. It is difficult to decide what initiates this explosive evolution of heat in the organism. Increased muscular activity, involving especially the musculature of the chest and of the heart, and the friction caused by the convulsive twitchings in the limbs merely contribute towards speeding up the process of warming. By themselves these movements would not be suf-

ficient to raise the temperature more than a few degrees. Horvarth has actually shown that the most vigorous muscular convulsions provoked in rabbits by poisoning with strychnine never caused a rise in temperature of more than 4° C. But the temperature of a hibernating animal may increase 20° C. in less than an hour.

The figure on the opposite page representing temperature curves based upon Horvarth's experiments with susliks (*Spermophilus cit.*) permits to distinguish three phases in this warming up process coincident with their awaking from hiberation.

A preliminary phase of very slow rise in temperature is followed by a period of an extremely rapid warming process, the temperature continuing to rise afterwards at a slow rate until a normal level is again reached. The curve is distinctly of the S-type characteristic of the course of events in a number of biological reactions. The explanation of the S-like shape of the temperature curve is very simple. The vitality of the tissues is within certain limits proportional to their own temperature and the oxidative processes grow more energetic with the progressive rise of their inner temperature. The improvement in the oxidations in turn favors the evolution of heat. In the course of the first hour or so it is observed that there is only a slight rise in body temperature, about 3.5° C., but the rise in temperature intensifies the reactivity of the organism to such an extent that in the next hour the temperature rises 17.5° C. The further rapid progress of the rise in temperature is checked by the continually increasing loss of heat resulting from an enlivened peripheral circulation.

Kennaway thinks that the rapid evolution of heat incident to the awaking from hibernation is associated with a synthesis of purine bodies. He analyzed dormice before they commence to hibernate, also in the torpid state and again when they emerge from that condition and become once more active. In the latter case the temperature of the dormice increased from 6.3°–8.2° C. to 22°–34° C. within one hour.

In two lots, consisting each of twelve mice analyzed before hibernation, Kennaway found 10.58 and 11.58 mgs. of purine nitrogen per mouse, or 0.077 and 0.083 per cent respectively. In ten animals examined in the state of torpor the average amount of purine nitrogen per mouse was 10.9 mg., or 0.082 per cent. But in animals which had already emerged from their torpor and

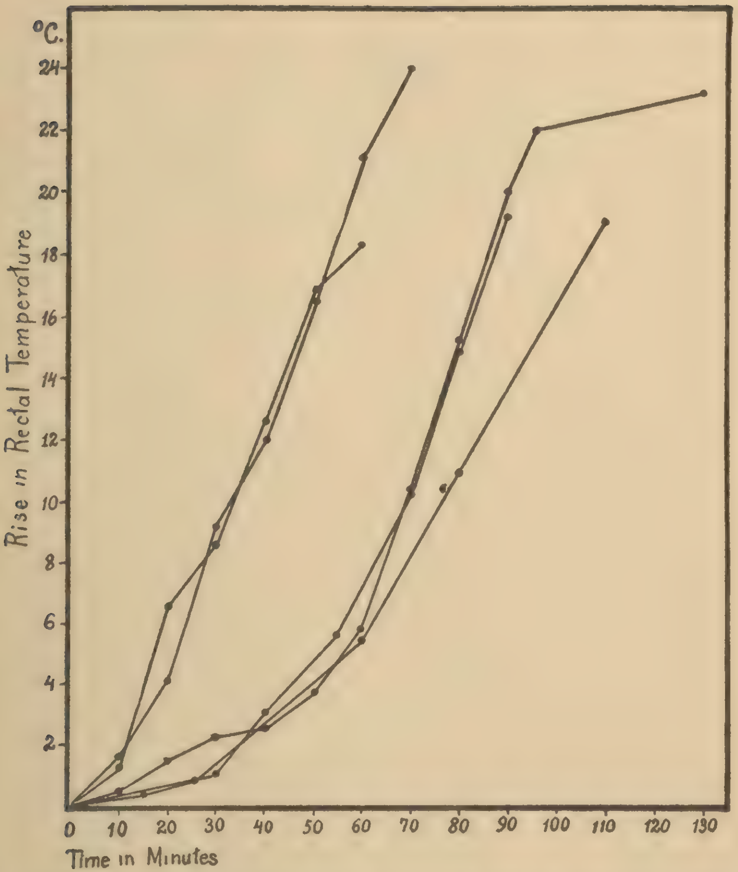

FIGURE 1.—A series of curves showing the rise in body temperature (rectal) of five susliks (*Spermophilus*) emerging from their winter torpor. The rectal temperature of these animals at the time of awaking varied between 8 and 14.8° C., and the outside temperature remained unchanged while the animals were warming up. (After data from Horvarth.)

were active the purine nitrogen was found to be 15.65 and 14.79 mgs. in the two groups of eight mice each which were analyzed. In other words, within two hours' time occupied by the process of awaking the purine nitrogen increased to 0.107 and 0.104 per cent respectively. Kennaway attributes this marvellous evolution of heat to the stimulating effect of the purines upon thermogenesis. The question, however, still remains open as to what factors bring about or make the purine synthesis possible just at that time, and the source from which they are derived in the animal's awakening from hibernation.

CHAPTER II

CHEMICAL PHENOMENA IN HIBERNATION

a. The Respiratory Exchange

The study of the gaseous metabolism is one of the most interesting and important chapters in the physiology of hibernation. The early researches of Regnault et Reiset, Valentin, Voit and others have disclosed phenomena the full significance of which is even now not well understood. Of the more recent investigators, Pembrey devoted much attention to this problem, but it is to be regretted that his experiments were not sufficiently controlled. Perhaps the best information, at least on certain aspects of the subject, can be obtained from Nagai's investigation, which is the most strictly controlled series of experiments with hibernating organisms.

The cardinal point in all studies of the respiratory exchange in hibernation, and one about which there has been also a great deal of debate, is the question of the respiratory quotient (i.e., the ratio between the volume of the expired carbon dioxide and the volume of inspired oxygen) which indicates the nature of the substances burned in the organism. According to experiments of the older observers as well as those of Pembrey in recent years, the respiratory quotient in hibernation may be as low as 0.2 or 0.3. Considering that the quotients corresponding to the oxidation of the physiologically important materials (fat, protein, carbohydrate) range between 0.7 and 1.0, such low quotients indicate very profound alterations of the chemical phenomena in the hibernating organism. In view of the great importance of the respiratory quotient it is essential that the methods by which it has been ascertained should be closely scrutinized. In this respect the work of Nagai stands quite isolated among the numerous similar studies inasmuch as it has been most adequately controlled.

The interpretation of these extremely low quotients has been associated with other hypothetical occurrences. Thus, Regnault

et Reiset to explain the occurrence of the low quotients resort to the findings, already referred to previously, that during deep sleep the weight of the hibernating animal shows usually small gains. The low quotient and the gain in weight is, according to their view, due to the same cause, namely, a retention and accumulation of oxygen in the organism. The hypothesis of the oxygen retention has been extended to explain also the facts of the marvellously rapid process of warming up during the period of awakening as well as of the long survival of hibernating organisms in the absence of atmospheric oxygen.

Dubois' analyses of the blood of three marmots in different conditions show that the oxygen content varies from 14.35 to 15.66 per cent, and he concludes that the arterial blood so far as its oxygen content is concerned remains practically unchanged in hibernation. Interesting experiments bearing on the problem of the utilization of stored oxygen for the warming up process during awakening from hibernation have been made by Henriques. He studied the respiratory exchange of the hedgehog while its temperature rose from 7.7° to 31.7° C. within two hours and fifty minutes. In this length of time the hedgehog consumed 2.213 liters of oxygen. On this basis Henriques computes that, assuming that fat alone had been oxidized, the rise in temperature resulted from an evolution of 10.4 Calories. The animal was killed quickly by a blow on the head and placed in an ice calorimeter to determine directly the amount of heat which the hedgehog possessed at the end of the awakening process. Since the average rectal temperature at the beginning of the awaking was 6.5° C. the total body heat when the animal began to emerge from its hibernation can be calculated from its weight (660 grams) and the specific heat factor of the body (0.83). The initial quantity of heat was, therefore, 3.561 Calories (0.83 x 660 x 6.5). The heat measured with the calorimeter was 13.412 Calories, so that the heat evolution coincident with the rise in temperature of 24° was 9.851 Calories. This corresponds very closely to the quantity which could be produced by the consumed oxygen (10.4 Cal.). It is therefore improbable that the warming up is accomplished with the aid of any stored oxygen.

It must be pointed out furthermore that on Regnault et Reiset's hypothesis the increase in weight should be continuous or at any rate permanent, while, as was shown in the preceding chapter, the positive variations in weight are transitory in

nature. Using Regnault et Reiset's data, Nagai calculates that 8640 c.c. of reserve oxygen could be accumulated by a marmot weighing one kilogram in the course of thirty days of quiet and uninterrupted sleep. This quantity should suffice to maintain the hibernating marmot alive for over two weeks in a nitrogen atmosphere, and for about fifteen hours when it is awake. Even this indirect reasoning, admitting that the facts were not to be questioned for purely technical considerations, shows that the logical working out of the hypothesis reduces the argument *ad absurdum.*

Pembrey sees in the low quotients an indication of a transformation of fat into glycogen, in which case a substance rich in oxygen is formed from one that is poor in oxygen. In a sense this is similar to Regnault et Reiset's hypothesis of a retention of oxygen except that the oxygen is assumed to be chemically bound and not stored away intermolecularly. Pembrey's interpretation rests on Dubois's hypothesis that glycogen is deposited in the liver during hibernation and serves as the source of the heat when the animal emerges from that condition. The formation of glycogen from fat involving an intramolecular fixation of the oxygen might likewise account for the rise in body weight, as was suggested by Bouchard in a different connection. Dubois's study on the progressive accumulation of glycogen in the liver during hibernation and its complete exhaustion in the brief period of awaking has been already referred to. Many observers likewise noted an accumulation of glycogen occurring in the hibernating organism.

Criticizing Pembrey's work Nagai points out very properly that his respiratory quotients (0.226–0.247) are even lower than could be expected theoretically. Even if there was no maintenance metabolism at the same time, the transformation of fat into glycogen—on the basis of Chauveau's formula—would require a respiratory quotient of 0.268, as can be seen from a consideration of the following reaction:

$$\underset{\text{Fat}}{2(C_{57}H_{110}O_6)} + 67O_2 = \underset{\text{Glycogen}}{16(C_6H_{10}O_5)} + 18CO_2 + 30H_2O$$

It is evident that 67 molecules of oxygen are required to transform two molecules of fat into sixteen molecules of glycogen, whereby eighteen molecules of carbon dioxide are set free. This would therefore give a respiratory quotient of $\frac{18}{67}$,

or 0.268. Considering that other reactions take place simultaneously in the hibernating organism for the upkeep of the body, the respiratory quotient should be much higher. This and other considerations of certain shortcomings of his method argue against Pembrey's experimental evidence, though the hypothesis is unquestionably meritorious.

The Dubois–Pembrey hypothesis postulates that the energy stored up in glycogen, produced in the course of hibernation, is again used up in the process of awaking, but this point is not definitely established. Were glycogen the only source of the energy consumed by the awaking animal it would be revealed unmistakably in the respiratory quotient. Opinions on this score, however, vary greatly, some (Marés, Henriques and others) claiming that the respiratory quotient of the animal on emerging from its state of torpor is typical for fat combustion, while others (Dubois, Weinland, etc.) maintain that the quotient tends to increase,—an indication that carbohydrate is oxidized in increasing quantities. In view of this contradiction definite conclusions must be postponed until we possess indisputable data. It is nevertheless highly probable that the results of Dubois's, Pembrey's and Weinland's studies represent the true condition of the metabolism in hibernation.

Hári denies the accumulation of glycogen in the hibernating bat. Reach, however, finds an increased amount in the liver. In frogs a maximum glycogen content is found in the fall. These facts suggest that the enzymes transforming glycogen into glucose are inactive, possibly owing to the low temperature, and for that reason the glycogen is not consumed during hibernation. Lesser's discovery that glycogen in frogs' livers exists in two distinct states seems to fit in with the above interpretation. In the winter Lesser found that the glycogen is in a stable condition and forms 1.4 per cent of the entire organism, but from April until June, in spite of rich nourishment, it constitutes only 0.2 to 0.4 per cent.

In the case of hibernating mammals the hypothesis that the inactivity of the enzymes is the cause of the retention of glycogen finds support in the investigations of Weinland and Riehl who maintain that the glycogen content of marmots remains practically constant during hibernation. In the brief period of the waking up, however, it quickly diminishes to one-half. From the tabulation of their results in the previous chapter (see p. 29)

it is clear that 1.69 gram of glycogen is lost per kilogram of marmot within the two or three hours of awaking. The respiration experiments performed by these investigators in which they found that the respiratory quotient was 0.94 corroborate their suggestion that the metabolism is chiefly of carbohydrates.

The subjoined table presents a summary of the results of Nagai's excellent respiration experiments. It is important to point out that while Nagai never found quotients as low as those reported by others, yet also in his experiments the quotients during deep sleep are invariably lower than 0.7 which is characteristic for fat oxidation.

Animal	*State*	*Per Hour and per Kgm.*		*Average R.Q.*
		Oxygen Consumed	*Carbon Dioxide*	
Marmot	Awake	605.5	486.0	0.804
	Drowsy	258.0	199.8	0.770
	Light Sleep	77.3	50.0	0.640
	Deep Sleep	30.5	18.7	0.610
Hedgehog	Awake	1527.0	1210.0	0.790
	Drowsy	298.0	228.0	0.765
	Deep Sleep	36.6	22.6	0.610
	Deep Sleep	58.9	38.2	0.640

Hári found that the respiratory quotients of hibernating bats vary from 0.552 to 0.696, and only exceptionally diminish to 0.50. Such quotients are also frequently observed in starving bats.

The low respiratory quotients found during the state of deep sleep gain further significance when the gaseous exchange is studied in connection with the animal's internal temperature. This relation is shown clearly in the table below:

NAGAI'S RESULTS

State of Marmot	*Per Hour and per Kgm.*		*Respiratory Quotient*	*Average Body Temperature*
	Oxygen	*Carbon Dioxide*		
Deep Sleep	30.5	18.7	0.610	10.0° C.
Light Sleep	77.3	50.0	0.640	13.5
Drowsiness	258.0	199.8	0.770	24.4
Wakefulness ...	605.5	486.9	0.804	36.5

It is interesting to compare these results with Valentin's, which I have recalculated for this purpose. In the following table the average value of a number of Valentin's data is given:

VALENTIN'S RESULTS

Deep Sleep	16.7	7.3	0.440	7.0° C.
Quiet Sleep	32.9	16.7	0.510	8.6
Light Sleep	100.7	63.4	0.630	
Drowsiness	402.2	288.5	0.720	
Wakefulness ...	680.5	545.6	0.800	

A glance at these two tables shows immediately that so far as the respiratory quotients are concerned there is remarkable agreement in the last three states of the animal. It is also evident that what Nagai designates "deep" hibernation corresponds to the state qualified by Valentin as "quiet" sleep. This is also borne out by a consideration of both the actual gaseous exchange and the animal's internal temperature. It seems therefore very probable that Nagai did not work with marmots in as deep a state of hibernation as Valentin did. The fact that the body temperature in Valentin's marmots was three degrees lower than that observed by Nagai certainly sustains the above conjecture, and this seriously weakens Nagai's criticism of the low quotients obtained by Valentin, since he had failed to reproduce Valentin's experimental conditions. Further research in this direction would be invaluable.

Horvarth already appreciated the importance of the gaseous metabolism, particularly in the study of the phenomena of awaking. Handicapped though he was by the imperfection of the methods available in his time, he nevertheless made valuable and true observations. His discovery that gophers (*Spermophilus*) produce thirty-four times as much carbon dioxide in the active state as when they are asleep is one of the first of this kind. A comparison of the metabolic rates in the different states of the hibernating animal is of great interest. If we designate the lowest amount of oxygen consumed and carbon dioxide produced per kilogram and per hour as *one*, Nagai's and Valentin's results form parallel series as shown in tabular arrangement on page 44.

It is thus evident that Valentin's data are considerably higher than Nagai's. The difference, however, is not as great as Nagai

State of Marmot	*Valentin*		*Nagai*		State of Marmot
	Oxygen	*Carbon Dioxide*	*Oxygen*	*Carbon Dioxide*	
Quiet Sleep	1	1	1	1	Deep Sleep
Light Sleep	3.1	3.8	2.5	2.7	Light Sleep
Drowsiness	12.2	17.3	8.1	10.7	Drowsiness
Wakefulness	20.7	32.7	21.4	26.0	Wakefulness

thought because, as was pointed out before, the condition of his torpid animal did not correspond to the condition of Valentin's used as the basis of this comparison. To avoid this discrepancy and to make the results of these two authors as nearly as possible comparable I rearranged their data identifying Valentin's designation "quiet" sleep with Nagai's "deep" sleep. On this basis we find that the active marmot produces 26 times (or 32.7 times according to Valentin) as much carbon dioxide and consumes 21.3 times (or 20.7 times according to Valentin) as much oxygen as the hibernating animal.

We will consider next the elimination of water through the lungs and skin. In the above cited case of the suslik, which was studied by Horvarth, the quantity of water given off in experiments performed during the waking and hibernating states was 0.098 and 0.014 grams respectively. In other words, the animal eliminated seven times as much water in the waking condition as it did in the hibernating state. Comparing this, however, with the elimination of carbon dioxide we find that the latter has been reduced almost five times as much as the elimination of water.

From the large number of observations made by Valentin on marmots the quantity of water eliminated per hour and per kilogram of body weight was on the average 0.028 or 0.029 grams, while the animals were asleep. The carbon dioxide produced by the same marmots varied from 0.014 to 0.091 grams according to the depth of their hibernation. In a state of drowsiness the animals eliminated 0.226 grams of water to every 0.678 grams of carbon dioxide.

We may conclude from this that, though the elimination of water is generally greatly diminished in hibernation, the elimination is relatively greater the deeper the sleep. These facts throw interesting light on the view held by Aeby and others that hibernation is associated with a dehydration process.

b. Protein Metabolism

The metabolism of matter in the hibernating organism has not received the attention it truly merits. There is undoubtedly a need for such extensive and complete metabolism investigations as have been frequently carried out with fasting animals. Disregarding casual allusions on this point in the literature, the only source of information at present is Nagai's work. We also owe to this investigator the first ray of light shed upon the very promising problem of the nitrogen partition in the urine of hibernating animals.

Nagai studied the distribution of the nitrogenous constituents in the urine by the phosphotungstic method. By this method the nitrogenous materials of the urine are separated into two portions: a precipitate containing the ammonia, uric acid, creatinine, purine bases and diamino acids; and a filtrate containing in solution urea, allantoin, creatine and the amino acids. By further treatment of both the precipitate and filtrate four fractions are obtained which, though representing mixtures rather than pure substances, are distinguished as the "ammonium," "diamino acid," "urea," and "amino acid" fractions. Under normal conditions the urea fraction is by far the largest in the urines of all animals. The following table which is reproduced with slight modifications from Nagai's publication contains the data on the distribution of the different nitrogenous materials, expressed in per cents of the total nitrogen excretion, in the urines of marmots in the hibernating condition as well as of those in a fed and starved condition.

Condition of Marmot		*Average Per Cent of the Different Nitrogen Fractions*			
		Urea	*Amino Acid*	*Ammonium*	*Diamino Acid*
A.	Hibernating	16.55	63.89	3.47	16.09
	Feeding	63.33	17.25	9.45	9.97
	Starving	66.20	22.00	4.70	7.10
B.	Hibernating	18.17	67.33	2.32	11.65
	Feeding	56.70	21.95	7.87	13.48
	Starving	63.20	16.90	3.90	16.00

Taking the average of the results for both marmots we find that the above four fractions of excreted nitrogen under different conditions arrange themselves as follows:

Nitrogen Fraction	*Hibernation*	*Normal*	*Inanition*
Urea	17.60%	60.02%	64.70%
Amino acid	65.60	19.60	19.45
Ammonium	2.92	8.66	4.30
Diamino acid	13.87	11.72	11.55

Studying the above data it will be noticed, in the first place, that the distribution of nitrogenous constituents in the urines of fed and fasting marmots does not show great variation except for the somewhat larger proportion of the urea fraction and a correspondingly lower proportion of the ammonia fraction, in inanition. The other two fractions are practically unaffected. The nitrogen distribution during hibernation presents an entirely different picture. The "amino acid" fraction which is otherwise only second in importance becomes the chief urinary constituent, while the "urea" fraction now occupies second place. This complete interchange between the "amino acid" and "urea" fractions is without parallel under any known physiological conditions. It points strongly to the assumption that the protein metabolism undergoes a radical change during hibernation, which may possibly be caused by the lowering of the metabolic activity in general.

It must be pointed out, however, that the proportion of amino acid nitrogen in the urine of fed marmots is higher than has been ordinarily observed. This may indicate striking peculiarities in the nitrogen metabolism of the hibernating animal which call for further investigation.

Probably the presence of large quantities of amino acids in the hibernating urine accounts for its strong acid reaction. Normally the marmot's urine is alkaline. Valentin also noted that the urines in hibernation are acid in reaction. Physiologically the excessive acidity of the organism is counteracted by an increased formation and elimination of ammonia and a withdrawal of basic substances from the tissues. In the hibernating marmot the "ammonium" fraction is, if anything, even less than in the fasting marmot. Although the facts necessary for a clear understanding are lacking, it may be conjectured that the elimination of a large quantity of amino acid nitrogen, while the quantity of urea nitrogen is very small and the "ammonium" fraction insignificant, are all the result of the failure of the hibernating organism to split off ammonia from amino acids.

We have no knowledge of the changes which take place in the fat or carbohydrate metabolism, but the fact that Dubois found aceton and Nagai lactic acid in the urines of their hibernating animals would make it seem highly probable that their metabolism is likewise affected.

Marmot "A" which hibernated 120 days excreted a total of 8.281 grams of nitrogen. Assuming that the average weight of this marmot was 2.7 kilograms, the nitrogen loss per day and per kilogram was 0.0255 grams. During inanition the same marmot eliminated 0.12 grams nitrogen. The nitrogen excretion during hibernation is therefore five times less than in inanition. The nitrogen elimination as compared to the elimination of carbon dioxide under the same circumstances is relatively large during hibernation, since, as has been shown before, the carbon dioxide production is diminished at least twenty-six times. It is not possible, therefore, to agree with Weinland and Riehl who maintain that in hibernation the marmot subsists on fat alone.

c. Mineral Metabolism

In view of the increased acid excretion through the kidneys it might be expected that there would be a noticeable change in the elimination of inorganic materials. Taking the sodium chloride elimination, however, Nagai finds a great decrease. Thus, the waking marmot excreted 427 mgm. of sodium chloride per day, and 31.7 mgm. when fasting. The same marmot during hibernation excreted only 6.6 mgm. per day.

A comparison between the nitrogen and sodium chloride excretion reveals some interesting points. The nitrogen elimination diminishes at a different rate, as the series of quotients tabulated below show. These represent the ratio between the nitrogen and sodium chloride in the daily urines.

Urine	*Hibernation*	*Inanition*	*Normal*
Total NaCl	1	4.8	64.7
N: NaCl	21.4	8.2	2.16
N: Cl	35.3	13.6	3.55

From this it is apparent that in proportion to the nitrogen loss the daily elimination of sodium chloride in hibernation is much less even than in fasting, indicating possibly a retention of sodium chloride in hibernation.

The results are quite different as regards the elimination of phosphorus. During normal activity Nagai's marmot excreted 39.7 mgm. P_2O_5 per day; in inanition the excretion was 23.9 mgm. and during the hibernating period only 15.6 mgm. per day. The relation of the phosphorus elimination to the total nitrogen excretion is demonstrated in the following table:

	Hibernation	*Inanition*	*Normal*
Total P_2O_5	1	1.5	2.5
N: P_2O_5	1.53	8.3	9.4

This shows that the phosphorus elimination during hibernation is not diminished to the same extent as that of the sodium chloride. It is difficult to decide what the source of the phosphorus is since in the organism it is found principally as a constituent of the nuclei and of the bones. Unfortunately we have no information regarding the effect of hibernation on the bones either from the histological point of view or from the point of view of chemical composition. The study of the mineral metabolism is still in its initial phase, but it should be pointed out here that the N : P_2O_5 ratio even for the normal marmot is rather unusual (see p. 165 on Mineral Metabolism in Inanition).

d. Metabolism of Energy

All phenomena of life are accompanied by an expenditure of energy, the amount of which is a measure of the intensity of the vital process. The energy equivalent of the organism's functions can be determined either directly by measuring the heat produced with a calorimeter or it may be computed indirectly from the energy content of the oxidized materials.

How great is the energy liberated daily by the hibernating organism? We may calculate this for Nagai's marmot "A" which hibernated 120 days as all the data necessary for this purpose are available. The marmot produced 2.105 grams of carbon dioxide per day equivalent to 0.5742 grams of carbon. The average daily excretion of nitrogen was 0.0255 grams equivalent to 0.1594 grams of protein with a content of 0.0836 grams of carbon. Subtracting the carbon derived from protein from the total carbon oxidized per day by the hibernating marmot (0.5742–0.0836) we find that 0.4906 grams were derived from fat. This amount of

carbon corresponds to 0.641 grams of fat. Knowing the energy equivalent of the combustion of a gram of protein or fat we are enabled to compute the daily energy loss from the above data:

0.1594 g.	Protein	$\times$ 4.1 =	0.6534	Calories =	9.9% of total
0.6410 g.	Fat	$\times$ 9.3 =	5.9613	Calories =	90.1%
			6.6147	Calories per day and per Kilogram	

We may conclude therefore that during hibernation the marmot expends daily 6.6147 Calories per kilogram of weight and that about one-tenth of this amount is derived from the combustion of protein and nine-tenths from fat (see chapter on Chemical Processes in Inanition).

The period of awaking which is accompanied by an unparalleled evolution of heat presents particular interest from the energetic point of view. It is still a more or less debated question as to what materials are being oxidized, some of the respiration experiments giving results approaching more nearly almost a purely fat metabolism while others indicate just as unmistakably a carbohydrate combustion. The radical disagreement between the findings of the different observers shows that there is room for further productive research in this line. It would take me too far from the subject under discussion to point out the objection to the technique employed in some of these studies.

Stated briefly, these are the two opposing views: First, the extraordinary development of heat is produced through the oxidation of glycogen in the liver; second, the heat is furnished by a combustion of fat. But apart from the question of the nature of the substances oxidized, the energy metabolism during awaking presents an extremely interesting problem.

Marés found in the case of a gopher (*Spermophilus cit.*) that while its temperature rose from 17° to 35° C. in one hour, the animal produced 1.135 grams of carbon dioxide and consumed 1.136 grams of oxygen. This gives a respiratory quotient of 0.72, and from this it follows that 0.39 grams of fat were oxidized during that hour. The amount of heat disengaged by the combustion of such an amount of fat (3.627 Cal.) would suffice to raise the body temperature 22.6° C. since the gopher weighed 193 grams and the specific heat of the organism may be regarded as equal to 0.83. The actual rise observed by Marés was only 18° C. Possibly this discrepancy between the theo-

retical rise in temperature and the rise actually found is due to an imperfection of the experiment which indicates a pure fat metabolism.

Weinland and Riehl have shown that a marmot under their observation produced 2.199 grams of carbon dioxide and used up 1.703 grams of oxygen per kilogram and per hour while it was emerging from the state of torpor. On the basis of the respiratory quotient (0.94) they assume that the gaseous metabolism corresponds to the combustion of 1.5 grams of glucose and represents a production of 5.5 Calories per kilogram and per hour. This quantity of heat would be quite ample to raise the body temperature of a marmot weighing three and a half kilograms 16.5° C. in three hours. Unfortunately these authors failed to measure the marmot's temperature before and after the awaking process and it is not possible therefore to tell whether or not the computed rise coincides more nearly with the actual temperature rise than was the case in Marés' experiments.

These two instances will suffice to make clear the intensity of the metabolic processes at the time the hibernating animal awakens from its sleep. In the case of the marmot under discussion the energy expenditure during hibernation (0.275 Cal. per kilogram and per day) is twenty times less than in the period of awaking (5.5 Cal. per hour). It may also be well to point out here that the energy requirement of an adult person is ordinarily one to one-and-a-half Calories per hour and per kilogram of body weight, while with twice that amount of energy some of the heaviest labor can be performed.

Since a large calory corresponds to 425 kilogram-meters of mechanical work, the energy produced by the hibernating marmot in 120 days could be utilized in lifting a person weighing 70 kilograms to a height of 4,800 meters, but if the energy production coincident with its awaking were maintained at the same rate for one day it would be sufficient to lift a similar person 800 meters.

CHAPTER III

PHYSIOLOGICAL PHENOMENA IN THE HIBERNATING ORGANISM

The profound changes in the chemical processes of the hibernating organism are accompanied by equally great modifications of its various functions. The present chapter is devoted to a consideration of this problem.

a. Respiration

The respiratory movements have been investigated by Spallanzani, Mangili, Saissy, Reeve, Hall, Valentin, Horvarth, Bougers, Dubois, Patrizi and Pembrey. From the extensive material concerning the respiration of hibernating mammals a few general facts may be selected demonstrating the peculiarities of the breathing process.

The rate of respiration is so slow that in deep hibernation there may be frequently only a single respiration in several minutes. As a rule, the inspiration is longer than the expiration. Horvarth observed in susliks (*Spermophilus cit.*) one to four respirations per minute and very often but one respiration in several minutes, whereas normally it performs 60 to 140 respirations. The inspiration is about four times as long as the expiration. It must also be mentioned here that hibernating animals can remain for very long periods without signs of discomfort in an atmosphere of pure nitrogen or carbon dioxide, or submerged under water. Marshall Hall says that he kept a hibernating hedgehog twenty-two and one-half minutes under water, during which time he was unable to detect any respiratory movements. Horvarth thinks that the respiratory movements are confined chiefly to the abdominal muscles and to the diaphragm, the thoracic muscles participating only very slightly in the respiration.

Pembrey distinguished four types of breathing according to

the temperature of the animal; in other words, according to its state of activity. Similar observations have been made earlier by Bougers. In a short note on the respiration of the hedgehog Bougers points out that it is of the Cheyne-Stokes type, i.e., it comes in groups of several movements separated by intervals of apnea of varying duration.[1] In very deep hibernation these intervals were found to last 30 to 45 minutes (!). The length of the intervening periods, however, as well as the number of movements in each respiratory group varied with the temperature of the animal. At the temperature of 10° C. the intervals of apnea lasted 33 minutes, and there were 16 respirations per group. As the temperature was gradually raised the intervals grew shorter and the number of respirations increased. By degrees the breathing became more frequent, though still periodic, the respirations occurring in groups of eight about every nine minutes. Ultimately, as the temperature rose to the normal level, it became quite regular and rhythmical, the animal having recovered from its torpor.

By injecting chloral hydrate Bougers was able to bring down the animal's temperature and induce sleep, but was not able thus to reproduce the phenomena observed in hibernation. The respiration grew slow and feeble but did not lose its rhythmicity.

b. The Circulation of the Blood

"Alle Erscheinungen der Bewegung der Blutmasse haben hier den Charakter der Ruhe, der es verröth, dass kein Sturm des Todeskampfes den Gang der Verhältnisse trübt." In these picturesque words does Valentin describe the flow of blood through the hibernating organism. A few sporadic contractions of the heart, possibly every three or four minutes or even less frequently, propel the sluggish stream of blood a short distance through the vessels, then the circulation presents again a condition of repose. Whereas in a rabbit the circulation completes one round in seven to eight seconds, it takes probably from three to four minutes in the hibernating marmot. The blood is practically withdrawn

[1] In his book on fatigue Mosso describes an interesting experiment on the respiration of eels during the winter season. At that time, he says, their breathing is no longer regular but occurs at intervals. "Sie athmen vier- oder fünfmal nach einander, dann bleiben sie längere Zeit, bis zu einer Viertelstunde unbeweglich, ohne Athem zu holen" (Die Ermüdung, Leipzig, 1892, p. 112).

from the superficial regions and is confined to the vessels of the deeply seated organs which in hibernating animals are usually of very large calibre.

During hibernation the blood is deprived of many of its cellular elements. Differential counts have shown that both red and white cells are greatly reduced in number, but Valentin's observation that the leucocytes are entirely lacking is doubtless erroneous. Rasmussen found very little change in the number of red cells, in the hæmoglobin or specific gravity of the arterial blood in hibernating woodchucks. The slight increase in the number of erythrocytes can be easily accounted for by a loss of water from the blood, but the size of the corpuscles does not change. The relative number of mononuclear and polynuclear cells is practically the same as in the waking animal but the total number of leucocytes in circulation decreases to about one-half in the torpid woodchucks. This decrease affects especially the lymphocytes. The scarcity of leucocytes in the hibernating blood is very probably due to their migration into the tissues of certain other organs, particularly the intestine. The general statement that the coagulability of the blood in hibernation is diminished is in keeping with the fact that a condition resembling hæmophilia has been frequently observed and that very profuse bleeding follows an injury. It is possible that this diminished coagulability is due to the excess of carbon dioxide in the blood but the subject would need further investigation.[1]

Owing to the very feeble exchange of gases in the organism the arterial and venous blood show almost no visible difference during hibernation. Rasmussen who studied extensively the blood gases of torpid and waking woodchucks maintains that this condition is rather exceptional, there being usually a marked increase in the amount of carbon dioxide in the venous blood in hibernation. The difference in carbon dioxide content between venous and arterial blood is 8.46 cc. in active animals and 13.69 cc. in the dormant woodchucks per 100 cc. of blood. The oxygen absorbing power (21.9 cc. oxygen per 100 cc. defibrinated blood)

[1] Couvreur found that the coagulability of the blood of snails during hibernation is diminished owing to the lack of fibrinogen (*C. R. soc. Biol.* 52, 1900).

Chio showed that the equilibrium of the calcium salts of the blood and the interaction of calcium with proenzyme to form enzyme depends on the carbon dioxide tension (*Arch. farm. sper.* 23, 206, 1917).

is not affected during hibernation, while the carbon dioxide carrying capacity changes from 223.3 cc. to 209.3 cc., the decrease being ascribed to a reduced alkalinity of the blood.

The blood pressure during hibernation is low, and Valentin mentions a case of which a marmot survived a lowering of its pressure to 16 mm. of Hg, which would invariably have caused death in other mammals. In the carotid artery of the marmot Valentin measured about 70 to 72 mm. of pressure with 2 to 6 mm. systolic oscillations. Dubois found the same pressure in the femoral artery of the marmot. As the animal wakes up and its internal temperature commences to rise the blood pressure also gradually increases to a maximum (body temperature about 24° C.) and then declines again.

Miss Buchanan investigated the electrocardiogram of hibernating bats, hedgehogs and dormice. The frequency of the pulse was found very much below normal. In the waking bat the pulse varies from 600 to 900 per minute, but when the animal was cold and quiet though not actually asleep the pulse rate diminished to 77 per minute, and there was also evidence of a 2 : 1 heart block. Similarly in the hedgehog the pulse rate, which normally varies from 280 to 320 beats per minute, was only 48 per minute though the animal was not even soundly asleep. In hibernating dormice evidence was found of a dissociation of the auricles and ventricles. In the very torpid condition the pulse rate fell to 12 to 30 per minute with only the ventricles beating (normal rate about 300). The electrocardiogram of the bat shows beside the "a" (auricular) and "v" (ventricular) electrical change, also an independent series "b" which is regarded as the electrical counterpart of auricular extrasystoles.

It is interesting to note that Miss Buchanan shows these "b" effects to be in some way related to the periodic breathing observed in hibernating animals. During the apnea period these "b" effects are absent. They disappear before the apnea begins, to reappear just before the respiration starts up again. She suggests as a possibility that blood changes known to affect the respiratory center are responsible for the presence or absence of auricular extrasystoles presumably represented by the independent series of "b" effects.

Macco found a similar prolongation of the auricular and ventricular systole and diastole of the turtle's heart during hibernation, and a slowing of the transmission of the impulse from

auricles to ventricles. The duration of the contraction was nearly twice as great in February (temperature 13.7° C.) as it was in June (temperature 26.2° C.). The height of the contraction was likewise greater during the warm season.

It should be mentioned, however, that working with the Alpine marmot, Hecht observed that the pulse frequency drops to one-fourth of the normal but there is no evidence of a heart block, only the transmission period increases causing a slowing up of the pulse rate.

Valentin observed in hibernating marmots a striking deviation from the normal condition, viz., that an inspiration is accompanied by a rise in the blood pressure which may either at once return to the original level or may remain high for some time. In the dog, for instance, an inspiration starts with a slight fall, and an expiration with a correspondingly small rise in the general blood pressure. The final effect, however, of an inspiration is to produce a rise in pressure and of an expiration a fall.

c. Thermogenesis and Thermoregulation

Pembrey has shown that young animals, whose nervous system is imperfectly developed at the time of birth, are incapable of regulating their body temperature. With the development of the nervous system its influence over the production and dissipation of heat also increases, and the internal temperature of the animal becomes independent of that of the environment. Even cold-blooded animals, whose temperature fluctuates with that of the external world can, according to Krehl and Soeteber, be compared to inorganic bodies only when the nervous system is eliminated. Between the homothermic animals, on the one hand, and the poikilothermic animals, on the other, the hibernating animals occupy a distinct position. They do not possess a normal temperature in the same sense as homothermic animals do. Simpson showed that the rectal temperature of the woodchuck (*Marmota monax*) varies from 33.6° to 41.2° C. This fact warrants grouping the hibernating animals in a separate class of heterothermic organisms. What relation exists between thermogenesis and hibernation?

Hibernating animals are peculiar in that they lack the ability to regulate their radiation of heat. Calorimetric studies of Dubois, Dutto and Monti give support to this idea. With the

lowering of the temperature of the surroundings their thermogenic power fails to compensate the loss of heat through radiation, but as the internal and external temperatures approach each other thermogenesis gains a relatively greater influence. This is evidenced by the fact that the internal temperature then usually remains somewhat higher than the outside temperature. It is a most significant fact that the lowering of the body temperature does not induce the state of torpor with all the accompanying symptoms of hibernation. Lowering of the temperature and sleep may be produced by injecting chloral hydrate but the resulting condition is materially different from hibernation as is seen from the character of the respiration. This has been also definitely demonstrated by Horvarth who performed numerous experiments on artificially cooling hibernating animals. These were cooled to 6° to 1.8° C. by plunging into ice water, but they recuperated quickly even after repeated trials without resorting to artificial respiration or warming. Horvarth thus failed to induce hibernation by lowering the body temperature. It is also a well known fact that land snails cannot be made to hibernate in the summer by subjecting them to a freezing temperature, but late in the fall, though the air is still quite warm, they actively prepare for the ensuing winter rest.

Hibernation comes and goes with the seasons and does not depend either on the temperature or stock of food. It is an intrinsic state of the organism, a phase in the rhythm of existence of the heterothermic organism. The animal commences to hibernate before its temperature falls and a state of torpor ensues. The awaking of the organism likewise precedes the quick evolution of heat. Quincke very poignantly observes: "Die Aenderung der Körpertemperatur folgt dem Kommen und Gehen der übrigen Schlafsymptome erst nach und bedingt nicht etwa dieselben." Quincke found that he could sever the spinal cord of a hibernating marmot in the neighborhood of the fifth vertebra without causing its death. A similar operation performed on a waking marmot would cause the body temperature to fall and would prove fatal for the animal. Even energetic stimulation of the soles of the marmot with the cord severed did not produce an appreciable rise in the body temperature. Quincke concluded from his experiments that: "In the brain of the marmot there is a caloric centre which so governs the organs of the body as to affect their metabolism and heat production inducing alter-

nately a state of activity or of hibernation; the respiration and circulation are affected only indirectly."

Dubois followed up Quincke's work trying to locate this "caloric centre" in the brain. In closing his book on the comparative physiology of the marmot he states his conclusions thus: "Situated in the lower wall of the anterior portion of the *aqueductus Silvii* there is a region the integrity of which is necessary in order that the alternate phenomena of torpor and activity, of lowering and raising the body temperature may occur automatically and in regular manner even after removing the hemispheres. If this region is injured or destroyed together with the midbrain the marmot may remain alive a long time, but it can now only sleep and breathe. It has lost the ability to awake."

Dubois' localization of the caloric centre has not been verified yet by other investigators. But supposing that a certain circumscribed area in the brain supervises the temperature fluctuations and regulates the heat production, it would still be unavoidable to assume that the cells of that particular section of the brain undergo cyclic, or periodic changes resulting in hibernation with its familiar effects.

d. Excretion and Secretion

In artificially cooled animals the movements of the abdominal organs cease entirely and it is fair to infer that a similar condition prevails in animals during the winter torpor (Horvarth). From time to time, however, as the animals wake up, they discharge fecal matter and pass urine. Animals fast asleep void urine about once in three or four weeks at which time they may also pass some fecal excreta. From Nagai's records it has been computed that a marmot excretes on an average less than five cc. of urine a day during hibernation.

In the stomach of marmots examined at the close of prolonged hibernation (over five months) Valentin found small quantities of a grey mass. In recent years the Montis have likewise studied the gastric content of hibernating marmots. The fluid, 2.5 to 5 cc. in quantity, gives an acid reaction and contains flakes which have been identified as epithelial cells. The total acidity of two stomach contents was found to be 1.3 and 0.79 per mille respectively. Valentin invariably found a weak reaction for bile pigments. The small intestine is usually empty and free from

mucus. The cæcum is large and contains an alkaline liquid full of mucous filaments.

The flow of bile continues uninterrupted throughout hibernation. Valentin observed in every marmot autopsied that the gall-bladder was greatly distended with bile which during hibernation becomes more condensed. As will be shown later, the continuous secretion of bile occurs also in inanition.

e. Reaction of the Muscles

The earliest experiments were performed by Valentin who observed that the irritability of the muscles was retained many hours after death if the animal has been killed while hibernating. He also noted that the contraction and relaxation of the muscles proceeded very slowly and, furthermore, that a few consecutive stimuli would suffice to produce complete tetanus. Patrizi observed that the shortening and subsequent relaxation of the muscle of a hibernating animal lasted three times as long as that of a similar muscle from the waking animal. The latent period in the former instance was likewise twice as long as normal. Similar observations were also recorded by Dubois.

The latent period of contraction of a hibernating muscle is much increased and is in direct relation to the internal temperature. The prolongation of the period of insusceptibility is an indication of the general functional inertness of the hibernating organism. Chapman found the latent period for the *extensor digitorum* of the hind leg of echidna to be 0.06″ at 3° C. and 0.01″ at 30°C. Recently Gayda investigated the problem of the effect of temperature on the contraction of the isolated gastrocnemius muscle of the hedgehog. The table presents some of his data:

Temperature	*Latent Period*
0° C.	0.129″
15	0.018
30	0.0088
35	0.0085

The significance of these figures will be better appreciated when it is recalled that the latent period for the gastrocnemius of the frog at 15° and at 30° C. has been found to be 0.0065 and 0.0033 of a second respectively (G. F. Yeo, *Jour. Physiol.*, 9, 425, 1888).

The curve of the simple contraction, apart from the latent

period, shows two successive phases, contraction and relaxation, which are usually very nearly alike. The total duration of a single contraction of the gastrocnemius of the frog is about 0.1 of a second. Gayda made very interesting observations on the effect on the simple contraction curve of either cooling or warming the gastrocnemius of the hedgehog, which are partly recorded below:

Temperature ° C.	*Duration in Seconds*		*Total Duration in Seconds*
	Contraction	*Relaxation*	
0	4.506	5.971	10.477
15	0.217	0.285	0.502
30	0.086	0.062	0.148
35	0.080	0.052	0.132

The results obtained by Rollet with muscles of bats and by Chapman with the muscles of echidna differ from the above by showing a much greater duration of the single contraction.

Tetanus is very easily induced in the muscles of hibernating animals. Patrizi found that five consecutive stimuli are sufficient to completely tetanize the muscle of the marmot, whereas if the animal is awake or artificially warmed the muscle responds to each of the stimuli by a separate contraction. Gayda finds that 1.05 stimuli per second produce complete tetanus at 0° C. while at higher temperatures a much greater number of stimuli and at smaller intervals are necessary to produce such an effect. Thus, at 30° C. twenty-four stimuli per second and 0.042 of a second apart are required.

The amount of work performed by a muscle of a hibernating marmot is very greatly reduced (Dubois), being at best only a tenth of that done by a muscle of a waking marmot. Furthermore, the muscle from the hibernating animal liberates less heat in its reaction to the same stimulus and with the same load.

It may also be pointed out that Kronecker found that the gastrocnemius of the frog produces 2700 contractions with a load of 20 grams in the summer, but only 250 contractions in the winter, when the muscle also goes very easily into contracture and but slowly recovers its original length. (Ueber die Ermüdung und Erholung der Quergestreiften Muskeln, 1871).

f. Irritability of the Nerves

Valentin discovered that the rate of propagation of the nerve impulse in hibernating marmots is only one meter per second. In warm-blooded animals the rate of travel of an impulse through the nerve is many times more rapid and even in the frog it is about twenty-eight meters per second. As soon, however, as the animal awakes and its body temperature rises several degrees the propagation rate of the impulse through the nerve increases in a marked degree.

Our knowledge of the affectability of the peripheral nervous system in hibernation is very inadequate. There is some indication in Horvarth's observations on *Spermophilus* that in the condition of torpor the animals are not affected by auditory stimuli. We also have Grigorescu's testimony that in the hibernating frog the cutaneous sensibility is much diminished. Claude Bernard thought that the decreased susceptibility of the peripheral nervous system may initiate the process of hibernation. According to this view an insensitiveness to cold is responsible for the failure of the reflex reactions against excessive loss of heat from the body through radiation. It is more probable, however, and is more nearly in accord with the facts, that the diminished affectability of the nerves is the outcome rather than the cause of the lowering of the body temperature.

Guardabassi found that in the toad (*Bufo vulgaris*) during hibernation a strong electrical stimulus is necessary to bring about cardiac inhibition through vagus stimulation. This effect can not be simulated in the spring by cooling the toads to 5° C. During the season of normal activity a much weaker stimulus, less than one-third as strong as the former, suffices to cause vagus inhibition (11 cm. between the inductorium coils in hibernation as compared to 37 cm. in the normal condition).

Merzbacher's extremely interesting experiments on the resection of nerves of the bat are very significant. As long as the animals remain asleep and their body temperature is low no signs can be seen of degeneration of the injured nerves, neither anatomically nor physiologically. But as soon as the bats wake up and get warm again the degenerative process begins immediately. If, on the other hand, the degeneration had already started in a cut nerve while the animal was still active the

process is at once arrested and does not proceed further when the animal goes into hibernation.

g. Reaction to Drugs, Toxins, etc.

The hibernating animal responds to various poisons and injurious substances in a manner distinctly different from that shown by the same animal in the waking state. The resistance of hibernating animals to violently acting drugs, as well as their resistance to asphyxiation or to greatly diminished atmospheric pressure is the result of functional inertia which characterizes the various physiological aspects of hibernation.

The results obtained by different investigators who studied the effect of hibernation on immunity are not concordant, but the discrepancies may be due to the fact that the excessive manipulation occasioned by the need of making injections, etc., interrupts the continuity of the hibernation. Billinger studied the immunity of hibernating animals towards bacterial infections, choosing for this purpose organisms whose optimum temperature is considerably above that of the hibernating animal. Though not very conclusive, these experiments show that the bacteria may survive within the organism of the host better than in an artificial medium. Inoculated with tubercle bacilli the animals revealed no symptoms while they remained asleep, but upon awaking they immediately developed the disease and died in a few days.

Blanchard experimented with a variety of toxins, venoms and parasites and arrived at the conclusion that the susceptibility of the hibernating animals was not materially diminished. Similarly Bertarelli, who experimented with rabies, anthrax, tubercle bacilli and diphtheria toxins found no evidence of an increased immunity. This author made the very important observation that with the onset of hibernation (marmots, dormice and bats) the alimentary tract becomes practically free from bacteria and the small intestine becomes actually sterile. The complete disappearance of the germs from the stomach requires at least a week. The intestinal flora at once assumes the usual composition when the animals awake and take food, but the rapidity with which the intestinal tract frees itself again of microörganisms when they fall asleep is truly remarkable. This is frequently accomplished in two days and the intestine once more becomes sterile.

Valentin found that marmots remained alive 132 minutes after an injection of curare sufficient to kill a rabbit of equal weight in five minutes. Similar observations were made with other drugs. Thus, a ten per cent solution of veratrine acetate which would kill a rabbit in 15 minutes required five times as long, or 75 minutes, to kill a hibernating marmot. Even the death of a poisoned hibernating animal reveals that its reaction is essentially different. Violent cramps and convulsions generally accompanying the death struggle of a poisoned animal are the organism's reaction to the detrimental agent. They are entirely absent in the hibernating animal which passes away slowly and quietly.

Studying the effect of substances which require an "incubation period" such as colchinin, saponin and tannin Hausmann found that during hibernation under the influence of the cold this period is greatly prolonged.

h. Tissue Repair

During the winter torpor the processes of growth and of tissue regeneration are held in complete abeyance. Even after several months of hibernation there is very scanty growth of hair shaved off from different regions of an hibernating marmot (Valentin, Beitrag VIII) and the claws and teeth do not grow at all. Injuries to the skin are not made good. "If an incision is made in the skin of a marmot during its sleep a slight bleeding occurs where the larger vessels are cut. The edges of the wound soon dry up but no suppuration takes place anywhere. Ultimately one merely finds a scar in the wounded region" (Valentin). Operations on nerves and bones show likewise that regeneration of the tissues is impeded by the sluggishness of the metabolic processes.

All observations on the physiological phenomena in the hibernating organism indicate that the vitality is at the very lowest ebb, the threshold between life and death being narrowed to a minimum, but the effects are produced by the lowering of the body temperature rather than by the protracted inanition.

CHAPTER IV

MORPHOLOGICAL PHENOMENA IN THE HIBERNATING ORGANISM

The microscopical investigation of various tissues and organs of hibernating animals furnishes a few additional strokes to the general picture of the suspension of activity already sketched in the preceding pages. Every tissue examined presents a condition of complete rest and no proliferation of cells is observed anywhere. Even the response to injuries is feeble and slow. Hansemann sloughed off portions of the nasal mucous membrane from sleeping hedgehogs and noted that leucocytes collected in the affected region but mitoses did not appear for four or five days. R. Monti, who has had extensive experience with the morphological condition prevailing in the hibernating organisms, formulated the following generalization:

"The proliferation of cells is entirely suspended during hibernation but immediately after awaking the tissues are renewed with unusual promptness and intensity, the organism speedily ridding itself of the old cells. This renovation of the cellular elements takes place even in such organs as the liver, pancreas, kidney and gastric glands whose tissues are otherwise characterized by great stability."

a. The "Hibernating Gland"

The so-called hibernating gland undergoes very marked transformations during the winter season. Hansemann proposed to call it the hibernating organ because of certain facts which made it seem improbable that it exercised any glandular function, but more recent investigation brought forth evidence which is sharply opposed to such a conclusion. The organ has been studied in a large number of hibernating animals and has been also identified in non-hibernating forms.

The organ is a lobulated, bilateral mass extending over the dorsal, cervical and axillary region of the body. Its lobules pass

also into the thorax and spread around the great vessels at the base of the heart and in the posterior mediastinum as far as the diaphragm. Occasionally much fat is deposited on the surface of the gland and is so closely mixed up with it that the two cannot be distinguished. It has a characteristically brown color which Affanasiew erroneously ascribed to hæmoglobin. It has no connection with the thymus.

Hatai discovered in the human embryo a gland-like structure —*glandula interscapularis*—which he believed to be the homologue of the hibernating gland, to which it corresponds both in position and in color.

Recently Cramer [1] described a glandular type of adipose tissue found in all embryos which after birth acquires the appearance of ordinary fatty tissue. In hibernating mammals this gland-like structure is retained through life. It is very vascular, rich in cholesterol and other lipoids, and functionally it is different from fat being related more to such endocrine organs as the thyroid or the adrenal.

In hibernating mammals the organ is not made up of typical adipose tissue. Hansemann pointed out that the cells contain numerous fat droplets but the cells themselves are polygonal and nucleated. The nuclei are never eccentric in position or flattened against the cell wall as is the case in typical fat cells. The hibernating organ does not undergo involution during the winter but its reserve material is gradually exhausted, the size of the organ diminishing in proportion to the decrease in size of its cells. Carlier found that in the hedgehog the volume of this organ attains a maximum towards the end of October, i.e., about the time when the animal begins to hibernate. At that time it constitutes three per cent of the total body weight. From that time on until the end of April or May it progressively atrophies, but afterwards, during the summer, the cells again begin to enlarge.

The lobules are made up of elongated polyhedral cells containing fat globules of various sizes entangled in the protoplasmic meshes. Each lobule is surrounded by a thick fibrous capsule in which lymphatics, blood vessels and nerves ramify. The figure represents a section of the hibernating organ as it appears before the winter sleep. The cells are about 30 to 33 micra along the long axis. The nuclei measure about 6 micra,

[1] *Brit. J. exper. Pathol.*, 1, 184, 1920.

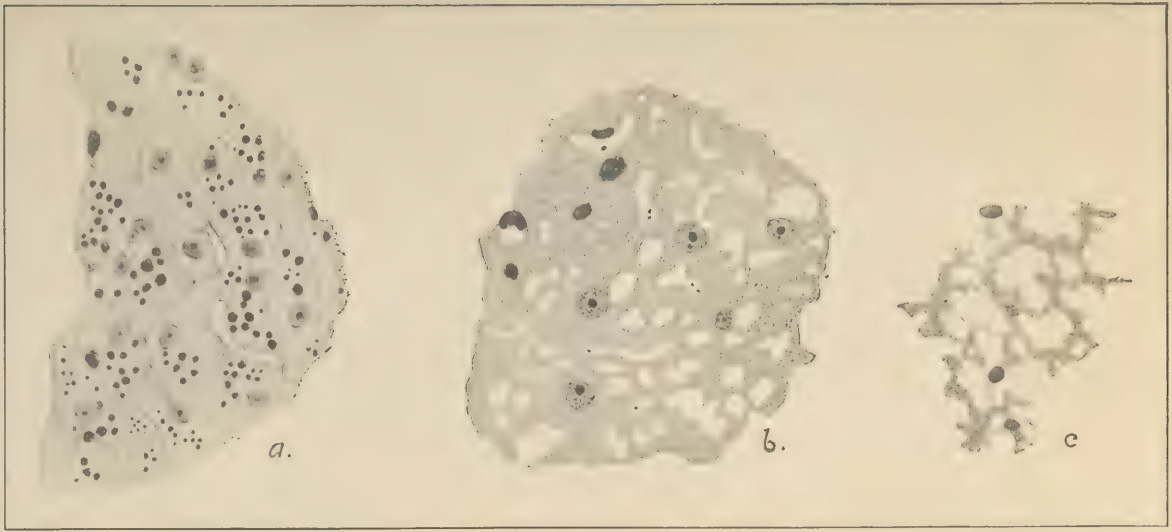

FIGURE 2.—Three stages in the transformation of the "hibernating gland" during winter sleep. (After Carlier.)

are rich in chromatin and take stains readily. The cells originate from small granular connective tissue cells at the margin of the lobule. As these cells enlarge they lose their round shape and become polyhedral owing to the pressure they exert mutually; at the same time the fat droplets multiply in number.

The first changes in the organ are confined to the protoplasm which becomes granular. The fat droplets begin to disappear while these changes in the cytoplasm are in progress, and a new substance sparingly soluble either in alcohol or in water fills the intracellular spaces. As a result of this the entire cell content is eventually converted into an homogeneous mass which is being carried away by the lymph stream and presumably serves as nutriment for the organism. The nucleus swells up and becomes spherical. Chromatic material is discharged into the surrounding protoplasm and ultimately the nuclear wall ruptures and the nucleus may disappear entirely. Shortly before the animal awakes the hibernating organ is reduced to a mere vestige, as shown in the figure, with but few cells remaining.

b. Microscopical Changes in Various Organs

The histology of the hibernating animals has not been completely worked out except in the case of the hedgehog, for which animal we have Carlier's extensive investigation of the histology of the various organs in both the waking and hibernating condition.

1. Digestive System.

The tissues of the tongue (of the hedgehog) lose their staining power and a similar deficiency in staining capacity is observed in the tissue of the stomach of this animal. The cells of the cardiac glands, which in the waking hedgehog show a strong affinity for acid anilin dyes, stain hardly at all during hibernation. The cells are small and granular. The cells lining the ducts are clear with nuclei situated near the base.

In the small intestines no radical changes except in the staining reaction have been noted. The cells of Lieberkühn's follicles are very clear and hardly stain with benzo-purpurine which usually imparts a deep hue to the cells of the villi of a waking animal. The number of goblet cells is increased during hibernation owing probably to an abundance of mucinogen.

The small intestine of the marmot was likewise carefully studied by Monti. The epithelial cells become narrow and prismatic with the nucleus in the middle. The free end of the cell bears a distinct fringe of cilia. Towards the free end the protoplasm is dense and reticular, but in the neighborhood of the nucleus and in the lower portion of the cell the reticulum is more open. The nuclei are oval and elongated, occasionally deformed in various ways by encroaching leucocytes. The nuclear wall is well formed but the chromatin is apparently not abundant. During the winter lethargy the goblet cells become very numerous. Their nuclei are triangular and the protoplasm usually granular.

The strongest contrast between the villi of a hibernating and of a waking animal is seen in the great number of leucocytes invading the former. Monti states that he found frequently as many as five in one cell, especially in the vicinity of the nucleus. Their protoplasm is almost unstained and their nuclei though variously shaped are rarely of the lobulated form. Polynuclear leucocytes occur seldom, the great majority being, according to Monti, small lymphocytes.

Carlier likewise describes this extraordinary migration of leucocytes into the mucosa and submucosa of the stomach and intestine of the hedgehog, but judging by the affinity shown by these migratory cells for the acid anilin dyes he believes that there were no lymphocytes among them. The leucocytic migration is observed to begin early in hibernation and the cells accumulate in such large masses, especially in areas traversed by blood vessels, as to give rise to heaps resembling solitary glands. In the foregoing it has already been shown that the number of leucocytes in the blood is continually diminishing during hibernation so that from 18,000 to 20,000 per cubic centimeter their number may decrease to 100 to 3,000. In the tissues they undergo degeneration and are removed by macrophages. When the animal awakes the proportion of leucocytes in the blood is rapidly restored by contribution from the lymph follicular tissue, such as the spleen and bone marrow.

Can any cause be assigned for this curious phenomenon? This is the answer which Carlier offers: "It has recently been pointed out (Bonchard, Essai d'une théorie de l'infection, *Proc. 10th Med. Cong.*, Berlin, 1890) that if the temperature of a warm-blooded animal be artificially lowered the microörganisms normally present in the intestine pass through the limiting epithelium

and invade the blood. This being the case, it is admissible to suppose that each succeeding year hibernating animals would run a serious risk of infection during the initial stages of hibernation by penetration of bacteria in their alimentary tract into the tissues. How long this risk may last would be difficult to say. Certainly during the first few days of the cooling process the risk can be very great. Further, this migration soon stops and the blood soon ceases to become poorer in white corpuscles as the cooling process goes on,—that is, after the animal has become too much cooled to favor the invasion of its tissues by microörganisms; and we find also that soon after the cessation of the migration of the wandering cells begin to degenerate giving with iodine green and eosin staining typical degenerative reactions pointed out by Heidenhain. Eventually they break down altogether, and are slowly removed by macrophages" (p. 98).

In a subsequent chapter a similar phenomenon will be discussed occurring in the experimentally fasting organism. The migration of the white cells there is likewise apparently associated with an increase in the permeability of the mucous epithelium allowing free passage into the tissues of intestinal bacteria.

In the liver of hibernating hedgehogs golden yellow pigment granules are found in the protoplasm. These are so arranged that they are most abundant in the portion of the cells which is toward the lumen of the bile ducts. Analyses have not revealed any iron in these granules, but granular masses found scattered here and there in the capillaries and recognized in both marmots (Quincke) and hedgehogs (Carlier) have been shown to contain iron (blackened by ammonium sulphide). The liver cells themselves never give this iron reaction. According to Carlier during hibernation the blood pigment is carried by the blood into the liver where the pigment granules are taken up by the cells and, being deprived of their iron content, are passed out through the bile ducts as biliary pigment.

Leonard studied the seasonal changes in the frog liver and came to the conclusion that generally speaking the yearly cycle presents two distinct periods: a growth period, from July to December, and a period of decline, from December to June. The average length of the liver cells varies very much during these periods, being smallest in April, and largest in November. It is also worth mentioning that the pigment accumulates during the winter season and disappears again in the summer. Morgulis

observed a similar phenomenon in livers from starving salamanders where the pigment content increases with fasting but vanishes rapidly when the animals are fed once more.

2. *Excretory System*

Monti found in hibernating marmots and hedgehogs that the tubules of the kidney are collapsed and their lumen very nearly obliterated. In the waking condition of these animals the tubules are widely distended. The nuclei are round, with a poorly defined reticulum of chromatin and are situated in the basal portion of the cells. In hibernating bats Baroncini and Baretta noted certain interesting modifications in the kidney. They described the appearance of fat globules in the convoluted tubules, a phenomenon which they never saw in the kidneys of waking animals, and a gradual swelling of the epithelial cells which becomes more pronounced with the progress of the hibernation. As will be shown later, the convoluted tubules in kidneys of fasting animals are generally vacuolated and it is possible that the swelling observed during hibernation is likewise associated with vacuolization. Baroncini and Baretta found no changes in the collecting tubules, which also corresponds with our observations of fasting animals.

3. *Spleen*

Mann and Drips have shown that in spermophiles the spleen undergoes no noticeable changes during hibernation, except that already within twelve hours the organ of the torpid animal becomes markedly congested: it becomes large, dark in color and its tissue friable. The congestion reaches a maximum in a few days and persists for about forty days. The amount of blood then begins to diminish and after seventy-five days does not exceed that in the normal spleen. Miescher found that the spleen of the Rhine salmon may also increase in volume owing to an accumulation of blood, which he considers to be a compensatory arrangement in the blood supplying function of the circulation.

4. *Glands*

Peiser studied the effect of hibernation on the thyroid. He found that in bats and hedgehogs the follicles are of the same

diameter in both the waking and hibernating condition. The follicular cells often become exceedingly small, the protoplasm appears much attenuated and the cell limits very indistinct. The nuclei are generally large in proportion to the cell, measuring 1.5 to 2.5 by 3.5 to 6.5 micra. The nuclei become drawn out along one axis in consequence of the flattening of the cells. Owing to their relatively large size the nuclei cause the sides of the cells to bulge out. The intrafollicular colloid substance is much shrunken. Mann, however, found no differences between the thyroids from active and hibernating spermophiles.

The morphological changes observed by Gemelli in the hypophysis of hibernating marmots are very significant in view of the importance which Cushing ascribes to this gland in connection with the phenomena of hibernation. The gland consists normally of two kinds of cells: chromophiles and chromophobes (neutrophiles) according to their affinity for coloring substances. The former are again represented by two distinct types: acidophilic, or eosinophilic staining with acid dyes, and basophilic or cyanophilic. Gemelli distinguishes also a third, transitional type of cell. The acidophilic cells are round with an eccentric nucleus and numerous small granules, and are commonly seen on the periphery of the gland. The cyanophilic cells are larger, with small intensely staining nuclei and granular protoplasm strongly vacuolated around the nucleus; these occupy the central portion of the gland. The transitional cells are longer and more or less irregular with a big nucleus which may be either central or eccentric in position. The protoplasm stains with basic dyes, but contains also acidophilic granules staining with eosin.

In hibernation the chromophobic cells remain unchanged numerically as well as in form, size or affinity for stains. But the cyanophilic cells diminish very markedly while the transitional cells increase in number. With the return to a higher plane of functional activity upon awaking the chromophilic cells multiply rapidly by mitotic division.

In his most enlightening book on the disorders of the pituitary body Cushing draws a parallel between the syndrome of hypopituitarism, or pituitary insufficiency, and hibernation. In both instances a seasonal somnolence is accompanied by subnormal temperature, slow pulse rate and retarded tissue oxidation. Though admitting that the assumption is only conjectural, he is inclined to believe that the hypophesis may, by becoming func-

tionally dormant, affect the metabolic processes. He says in this connection: "In clinical conditions of hypophesial deficiency somnolence is a conspicuous feature. It is suggestive, at all events, that in both the physiological state of hibernation and the pathological condition of hypopituitarism there is a tendency towards unwonted sleep, a subnormal temperature and slowed pulse, a lowered metabolism with diminution of carbon dioxide output, a definite hypæsthesia of the body to painful stimuli, and in the males at least, an hypoplasia of the sexual glands. In the clinical states, moreover, these symptoms can be largely alleviated by glandular administration" (p. 233).

This idea of the possible control over seasonal functions by the ductless glands may yet prove very fruitful in future researches on the nature of hibernation. In this connection it may be pointed out that the organ generally called the hibernating gland may be concerned with the production of some internal secretion, and experiments with this in view have already been mentioned in the foregoing. Considering the striking changes that appear in different structures during hibernation, it would seem unwarranted to regard Cushing's idea as established beyond a doubt. From the evidence we at present possess it is no more justifiable to ascribe a controlling influence to the hypophysis than to any other organ of the body.

The recent very extensive inquiry into the condition of the ductless glands of hibernating spermophiles (Frank C. Mann) leads to the same general conclusion. Mann studied the seasonal variations in the finer structure of the sex glands, thyroid, parathyroid, thymus, islands of Langerhans, the pituitary and the adrenals. In some of these he failed to observe any change during hibernation, while in others he observed changes in staining capacity or cellular arrangement of greater or less significance. The most important part of his research is, however, the experimental wherein he shows that the extirpation even of those glands which do undergo seasonal variation in no way interferes with the normal course of hibernation.

Before concluding this section on modifications appearing in the glandular structures mention should be made of Krahelska's investigation of the albumin gland of land snails. There is no measurable difference between the glands before or during hibernation. If, however, the winter rest is artificially prolonged, up to even fifteen months, changes appear in the cells of the

gland resembling the degenerative phenomena occasioned by advanced inanition. But while in experimental inanition the secretory granules are completely used up in about three months, these may still be present at the end of fifteen months of suspended animation.

c. Bone and Marrow

The differential blood counts have shown that the white cells suffer a relatively larger reduction in number than the other cellular elements of the blood in the course of hibernation. It has also been pointed out that this is due to a migration of the leucocytes into the tissues of the internal organs.

Poppenheim made a thorough survey of the morphology of the blood and of bone marrow of spermophiles before, during and immediately after hibernation. The blood of this animal normally contains no nucleated red cells. There is neither hydremia nor an apparent condensation of the blood. The changes in the volume of the blood are rather adaptive to the organism's needs, the volume decreasing as the intensity of the oxidative processes in the organism diminish. The changes observed in hibernation in no manner, however, indicate a condition of anemia. Upon awaking the volume of blood again rapidly increases, the blood therefore appearing hydremic; no nucleated red cells are found at this stage.

The bone-marrow (particularly that of the ribs) is only partly fatty. The erythrocytes are represented by a few megaloblasts, or large nucleated red cells, and numerous normoblasts (small nucleated cells). Numerically, however, these are subordinate to the leucocytes of which there are eosinophile polynuclears and basophile mononuclears, eosinophile myelocytes, mononuclear and polynuclear mast cells, also large and small lymphocytes. Granular leucocytes predominate over the non-granular type.

During hibernation the marrow of the ribs still contains but little fat, but in the long bones the marrow is completely transformed into fat. It is likewise important to note that hemosiderin —an iron containing decomposition product of hemoglobin— of which there is normally very little present in the marrow is found in large quantities during hibernation. In some instances Poppenheim observed that the marrow of the tibia was edematous (gelatinous) and this observation is of interest because, as will

be seen later, this is a common occurrence in experimental inanition.

Soon after awaking from hibernation the bone-marrow presents an entirely new picture. It becomes again typically red, with erythrocytes in preponderance, and with polymorphonuclear leucocytes predominating over the mononuclears. Large lymphocytes and young megaloblasts are very abundant, displaying a great number of mitotic divisions.

d. The Nervous System

In view of the fact that the loss in weight sustained by the nervous system is quite insignificant even at the end of several months of hibernation, it is not surprising to find that the morphological changes are slight and apparently of little importance. The changes which have been observed are typical not only for the condition of rest but also of inanition in general.

Baroncini and Baretta observed disintegration and gradual diminution of the chromatic substance in cells of the anterior and posterior horns of the cord as well as in the pyramidal cells of the cortex of bats. The contents of the nuclei is shrunken and concentrated around the nucleolus. In advanced stages the nuclear wall may even completely disappear, the nucleoli migrating out either into the cytoplasm or outside the cell (spinal cord). This accounts for the frequent occurrence of many nerve cells without nucleoli at the close of hibernation. The staining becomes faint and diffuse.

Levi believes that there is a difference in the manner of modification of the nervous system in hibernating mammals and amphibians. In the former he observed no changes whatsoever, whereas in the hibernating cold-blooded animals he found that the distribution and the micro-chemical reaction of the chromophil substance is seriously affected. The latter continually diminishes in quantity during hibernation, but reappears when the animal awakes.

Levi's results pertaining to the hibernating mammal have not been corroborated by others. In the first place, Levi studied only a single dormouse. The chief reason for the discrepancy, however, is to be found perhaps in the fact that the sleep of the dormouse is frequently interrupted, the animal waking up sometimes every twenty-four hours to take food. We already alluded

to the studies of Baroncini and Baretta on bats. Legge also found that the Nissl bodies disappear from the cytoplasm of the nerve cells of hibernating bats, the cells being frequently honeycombed with numerous minute vacuoles.

Zalla found that in various hibernating animals (mammals, reptiles) the chromophil substance and the endocellular neurofibrils behave independently of each other. The neurofibrils are fine and very numerous in the waking state but in the course of hibernation they become coarse and fewer in number. Tello likewise found the neurofibrils of the motor cells of the spinal cord in hibernating lizards to be thicker than usual. Dustin regards this thickening of the neurofibrils an adaptive phenomenon whereby, through diminished resistance offered to the conduction of the nervous impulses, the function of the nervous system is maintained effective when the organism's available energy is exceedingly limited. The thickening of the fibrils is, however, apparently a general response to a lowering of the temperature as is indicated by the researches of various neurologists (Cajal, Marinesco, Dustin).

Zalla could discover no morphological change in the Nissl substance of dormice, though a distinct diminution was demonstrable in the hibernating reptiles. Marinesco maintains that the Nissl bodies in Purkinje cells of hibernating hedgehogs decrease and become diffused throughout the protoplasm. Rasmussen and Myers, however, could detect no changes in the Nissl granules of marmots which they could regard as characteristic for the hiberating condition.

The condition of the morphological elements of the nervous system during hibernation is therefore as much a controversial point as that in experimental inanition, to which we will return in a later chapter.

CHAPTER V

METAMORPHOSIS

The development from the egg to the adult form is accompanied in many organisms by very striking changes in structure and function. These changes are more or less abrupt, being generally in the nature of an organic crisis. Thus in insects the transformation of the pupa into a butterfly is preceded by a series of profound alterations in their digestive organs as well as in the muscles, the former being completely destroyed and absorbed, and new structures arising in their stead. The nervous system is only slightly modified, while the sexual glands remain entirely unaffected.

The Mexican axolotle at a certain stage in its development loses its gills and giving up the aquatic mode of life becomes the terrestrial Amblystoma. Yet these two forms of the same organism are so different in appearance that they have long eluded identification as the larval and the adult phase in the development of the same salamander. The identification has been made especially difficult because the larval axolotle frequently attains a larger size than the Amblystoma and may even become sexually ripe and breed, while still remaining in the water and retaining permanently the larval characters. Marie von Chauvin observed that with the approach of metamorphosis the axolotles refuse to take food, and when they leave the water they are in a state of inanition. More recently Powers has shown experimentally that scarcity of food, or its temporary withdrawal, is the only condition under which metamorphosis is inaugurated, probably owing to the influence it exerts upon the autolysis of the tissues.

Bohn likewise showed that an abundance of food, while favoring the growth of tadpoles, usually retards their transformation into frogs. A sudden suspension of feeding invariably leads to a prompt metamorphosis. It seems that inanition, complete or even partial, brings on the physiological crisis which leads the

animal into a new phase of existence. We may recall that Barfurth had already recognized the stimulating effect of inanition and its significance in the economy of nature.

The atrophy of the larval structures in batrachians is not a purely local phenomenon. The histolytical processes are of general occurrence affecting the organism as a whole, as the investigations of Barfurth, Loos and Bataillon show. Miss Kaufman describes changes of a profound character which take place in the cells of various organs of metamorphosing axolotles. The absorption of gills, fins and other larval structures is merely the result of their slight resistance to the histolysis. The studies of Schaper and also those of Romeis have demonstrated that tadpoles even prior to the metamorphosis begin to diminish in weight, the loss being very rapid and intense. It is therefore improbable that the inanition during the period of metamorphosis is the cause of the transformations, but rather a symptom and a manifestation of a widespread and deep-seated internal process. Recent researches have brought to light the relation between metamorphosis and the activity of the glands of internal secretion, notably of the thyroid gland. Miss Kaufman stimulated the onset of metamorphosis in axolotles by feeding with minute quantities of thyroidin, which caused a remarkable increase in the katabolism of the animal so that it was losing weight even more extensively than during complete inanition in spite of the fact that it was fed on a liberal allowance of meat. It may be concluded therefore that under conditions of a naturally occurring metamorphosis the effect of the inanition is that of an additive factor either intensifying the thyroid function or the katabolic processes initiated by it thus hastening the transformation. If the larva is subjected to starvation before the internal factors have developed their full force the result may be just the opposite and the transformation will be retarded. In other words, inanition acts as a stimulant when it comes at the proper physiological stage of the development of the organism and when the internal forces are ready. This may account for such experiments as those performed by Bataillon on tadpoles which were kept without food for eighteen months without, however, undergoing metamorphosis. It is very probable that the starvation began too soon and thus checked or even prevented the progress of those evolutionary changes which precede the metamorphosis.

The pupa stage of insects may last from a few days to several months and represents a condition of physiological inanition. The pupa stage in the development of insects is characterized by complete rest and inactivity, but within the outer shell the processes of transformation proceed slowly and incessantly. The energy is derived from the reserves of the body. The morphological changes accompanying metamorphosis have been extensively studied but the metabolic processes have been much neglected until recently, when the physiology and biochemistry of larvæ and pupæ have been successfully investigated by Weinland and, from a somewhat different viewpoint, by Tangl.

The pupation of the Calliphora fly studied by Weinland lasts 13 to 14 days. The weight of the pupæ diminishes because in the absence of food intake—except oxygen—they still continue to give off carbon dioxide and water. The elimination of the carbon dioxide during the pupation period is divisible into three distinct phases. The first, lasting only a few days, coincides with the active histolysis of the tissues. This phase is marked by a progressive diminution of the oxidative process. The next phase is characterized by a relatively stationary level and is followed by a period of very vigorous oxidation. During this last period the new musculature of the metamorphosed insect becomes active.

Tangl's observations on the pupæ of the fly *Ophyra cadaverina* correspond closely to Weinland's results. Tangl, however, found that the diminution of the carbon dioxide production commences already a few days before pupation when the larvæ cease feeding and fall into a state of inanition. As in hibernation, the metabolism of energy of the pupæ is very slight. The energy is almost entirely derived from fat. The table opposite shows the relative amounts of material lost during the different stages, assuming the loss sustained by the pupa to equal one.

It is worth observing that in the period just preceding pupation, when the larvæ cease feeding and are, therefore, in a state of inanition, the tissues do not become enriched in water content as is the case in experimental inanition. The larvæ become poorer in their content of water; in other words, this stage of their development is marked by dehydration.

During the six days of fasting preparatory to pupation a thousand larvæ lost 672 milligrams per day and of this 610 milligrams, or 90 per cent, is water. Of the remaining 62 milli-

Stage	*Loss Per Day and per Gram of Body Substance*			
	Water	*Dry Substance*	*Fat*	*Calories*
Larva	13.3	2.1	1.9	2.2
Pupa	1.0	1.0	1.0	1.0
Fly (first two days)	4.8	8.5	4.3	6.8
	Loss per Day and per Gram of Dry Substance			
Larva	9.2	1.4	1.3	1.6
Pupa	1.0	1.0	1.0	1.0
Fly (first two days)	5.5	11.5	4.9	7.8

grams 93.5 per cent is fat. The total energy exchange during that time is 0.62 Calories per day, or 10.05 Calories per day and per gram of dry substance. But in the course of metamorphosis, which lasts about a fortnight, one thousand pupæ lose only 76 milligrams of which 45.8 milligrams, or 60.3 per cent, is water, and the remaining 30 milligrams is fat. In other words, the lost dry substance in the pupæ is nothing but fat. The energy exchange is 0.282 Calories per day, or 9.34 Calories per day and per gram of dry material, which is further proof that the substance oxidized during pupation is purely fat.

CHAPTER VI

INANITION OF THE BREEDING SEASON

The Salmon

The most unique and at the same time the most remarkable instance of physiological inanition is that represented by the salmon. In the winter these fish migrate from the seas and swim up the fresh water streams. From the time they enter the fresh water until their spawning season is over, which in the Rhine salmon may last from eight to fifteen months, the fish take no food.

The story of the king salmon of the Pacific coast, the largest and finest among the salmonoids, is even more remarkable. After a prolonged and extremely exhausting upstream journey without food, the reproductive organs developing in the mean time at the expense of other tissues, these beautiful salmon reach their spawning beds, then spawn and die.

Compared to the salmon of the North Sea, whose stomachs and intestines are always packed with small fish, the digestive tract during the salmon's sojourn in the Rhine presents a striking appearance. The wall of the stomach and intestine is strongly contracted, the lumen being much reduced. There is no content save for an occasional pebble or some other object accidentally swallowed with the water. The gall bladder is almost always empty, but the intestine is generally colored with bile poured out directly into its cavity.

The mucous membrane of the œsophagus and intestine is very thin but resistant and never gives an acid reaction. It is quite probable that apart from bile no digestive juices are being secreted.

Paton reporting to the Fishery Board of Scotland on the life-history of their salmon corroborates Miescher's observations on the Rhine salmon. He offers also much evidence in favor of the view that the migrating salmon are in a state of complete

inanition. Extracts from intestinal and mucous membranes show poor digestive action, and the great increase in the number of putrefactive organisms indicates that no free acid is present in the stomach. It is especially noteworthy, as was brought out by Paton and his collaborators, that both the morphological changes in the lining membrane of the digestive tract as well as their studies of the activity of extracts indicating almost a complete cessation of the function of the digestive organs, all go to prove that the salmon cease to feed even before they start on their upstream migration. The seasonal movements towards the upper reaches of the streams—the original habitat of the salmon—for purposes of spawning may be regarded as being impelled by an instinct of preservation of the species. The migration downstream and into the wide expanse of the sea is in quest of food, and is therefore impelled by an instinct of self-preservation. If one may be permitted to speculate, the mystic instincts which periodically drive the salmon upstream and then again downstream are nothing else but the sexual hunger and the food hunger which alternately dominate its entire existence.

The inanition processes in the salmon are, of course, complicated by the circumstance that the body reserves are not drawn upon simply to supply energy necessary for maintenance but also to furnish material for the development of the gonads. The destructive processes are therefore more severe than in ordinary inanition; they are accompanied by constructive processes in the ovaries and testes which grow at the expense of the muscles. Furthermore, the enormous amount of energy used up for the mechanical work performed in the upstream migration is an additional heavy drain upon the animal's reserves.

Miescher maintains that in this progressive wasting of the body musculature not a fibre undergoes actual disintegration though its substance is being rapidly consumed. There results what Miescher characterizes as the "liquefication" of the muscles which he ascribes to impaired tissue respiration occasioned by a diminished vascular tonus. If this interpretation is correct, the great development of the ovaries may be regarded as being favored by the release of large quantities of building material into the circulation rather than to suppose that the breaking down of the muscle protoplasm is caused by the excessive requirements of the ovaries. Nussbaum's observations on the growth

of the sexual glands in starving frogs must also be considered from this point of view.

Paton computes that in male salmon 5 per cent of the muscle fat and 14 per cent of the proteins go to build up the testes, while 95 and 86 per cent respectively furnish mechanical energy. In the female, 12 per cent of the fat and 23 per cent of the protein derived from the muscle tissue are transported to the growing ovaries, while 88 and 77 per cent respectively are burned up for energy. In the late part of the migration season fats are used almost exclusively as a source of energy.

The flesh of the salmon in fresh water becomes greatly enriched in water content. Paton records that in the upper reaches of the streams the musculature contains five per cent more water than that of the estuary fish and that this difference increases to 13 per cent towards November.

C. W. Greene also records an increase in the water content of the flesh of the king salmon which he computes at 6.6 per cent on a fat-free basis. The organic extractives are likewise increased both in absolute amount and in proportion to the other constituents of the muscle substance. The ratio of the extractives to the proteins increase 50 per cent from the time the salmon commence their upstream journey until they reach the spawning grounds. These results agree closely with those of Lichtenfeld whose investigation of the composition of muscles of starving fish will be referred to in a subsequent chapter.

PART III

EXPERIMENTAL INANITION

CHAPTER I

ACUTE INANITION

It is a truism that the existence of an organism is jeopardized by continued abstinence from food. Existence, however, is not incompatible with a limited abstinence the extent of which can be determined by strictly experimental methods. Under "experimental inanition" we include, therefore, such instances of fasting which in the case of human beings are of voluntary choice and in the case of animals are due to a restriction imposed by the experimenter, but in either event the matter has been investigated by reliable laboratory methods.

The knowledge thus gained from carefully planned and supervised experiments demonstrates beyond peradventure the fallacy of our ingrained popular belief that life can be quickly endangered by fasting. It is also certain that those who have been exposed to starvation through occupational hazards, for instance, sailors or miners, have suffered less from privation than from mental agony which accompanied their suspense between life and death.

There are authentic records of human beings who endured complete abstention from food for over 60 days.. Kiesewetter relates that the Shravaks, a sect of religious mystics in India, undergo a yearly fast of from one to 30 days. In our own midst and within recent time several persons, described generally as professional fasters, have refrained from all nourishment for periods varying from 10 to 50 days.

Considering that an organism as highly organized as the human being can endure inanition for a number of weeks, it is not surprising that among the lower animals existence without food may extend over incredibly long periods of time. Jacquet reports (*Rev. Sc.* 3,540, 1895) that his scorpions fasted 368 days, and Blackwell (*Am. Mag. Nat. Hist.*, 15,237, 1845) observed that spiders survived starvation 17 months. Wodsedalek kept larvæ of the small beetle, *Trogoderma tarsale,* 1884 days,

or over five years without food, and during that time they were reduced to about 1/600 of their original mass. This observer noted that the time of survival depends directly upon the age of the beetle larvæ. Thus, one-fourth grown larvæ lived without food 14 months; one half-grown larvæ, about three years; and three-quarter grown larvæ, about four years.

Smallwood reports an extremely interesting case of a fish, *Amia calva,* which survived inanition for 20 months at the end of which time it was killed for purposes of histological study. Some of Chossat's frogs lived through 16 months of inanition. Collin and also Vaillant kept snakes without food for nearly two years.

It is obvious that the organisms deprived of nourishment must obtain energy, necessary for maintaining the functions upon which the continuation of their existence depends, from sources which are within themselves. In other words, they must draw entirely from their capital instead of their income to cover the current expenses of subsistence. What happens to the organism under such circumstances? How are the organism's composition, its functions, its structural elements affected by the deprivation of nourishment? In the following pages we shall attempt to answer these various questions.

a. Changes in Weight of the Body and of Separate Organs

The most immediate and obvious result of inanition is the diminution of the body weight which the fasting organism sustains from day to day. This continuous change in weight is the safest guide to the progress of the fast. It is also the best proof of the uninterrupted course of inanition.

Chossat's investigation of the loss in body weight was the first systematic attempt to gain scientifically controlled information on this subject. In his truly classical research he reached the conclusion that the maximum loss the organism is able to survive is about 40 per cent of the initial weight, at which time death from exhaustion usually supervenes. Since Chossat made his epoch-making contribution the matter has been studied more extensively and on a great variety of organisms. Chossat's dictum can no longer be accepted as we know that the final loss of weight depends on a number of causes, of which the initial composition of the organism is of no small

significance. The greater the store of fat in the body at the commencement of the fast the longer can the privation of food be endured and the greater may be the relative loss sustained. The literature on fasting abounds in instances of body losses of 50 to 60 per cent and even greater losses which various animals, both cold-blooded and warm-blooded alike, have suffered before death from starvation occurred.

There is only one case on record where it has been claimed that in spite of a protracted abstention from food the body weight remains unchanged. Moore and Herdman claim that lobsters kept in captivity without food retain their original weight even after eight months of fasting. This constancy of the body weight is, however, only apparent since the actual loss sustained by the dry matter is masked by an absorption of water. Furthermore, I have shown that, in spite of this circumstance, lobsters which were subjected to complete starvation for only 56 days showed a diminution in body weight of about three per cent.

It is believed by some that the body weight may increase transiently in the course of inanition. Bouchart by placing a fasting man on a self-registering balance of Redier observed that instead of the curve of loss in body weight declining continuously, it would rise from time to time indicating a gain in weight of 10 to 40 grams. These positive variations were purely temporary and were quickly followed by a further decrease. Bouchart considering the various possibilities, such as absorption of moisture or of carbon dioxide or of oxygen, etc., comes to the conclusion that incomplete oxidation of fat, resulting in the formation of glycogen, is the only tenable explanation for the occurrence of positive changes in weight, since a gram of incompletely oxidized fat would thus add 0.76 gram to the weight. Experiments performed with dogs yielded similar results, and although this fact of the occurrence of transient increments in body weight deserves careful consideration, we must for the present reserve judgment on this important question until the accuracy of the automatic instruments is beyond a doubt.

Falck, studying the curve of loss of body weight in starving dogs, found that following an abrupt fall in the first day of fasting the weight continues to decline rapidly during the second and third day, then the curve becomes practically a straight line with a gradual slope towards the abscissa. According to Manas-

sein and Okintschitz, both of whom experimented on rabbits, and Schimanski on chickens, the loss of weight in the last period of inanition reaches a maximum and the curve of the body weight, therefore, shows two abrupt drops, at the beginning and at the termination of the fast.[1] Lasarev, on the other hand, shows that the loss in weight of starving guinea pigs is very small during the last days. His curves, based on a very extensive material, resemble essentially those of Falck.

Does the change in weight from day to day, as the fasting organism continues to draw upon its resources, obey some definite mathematical law? Luciani thinks that the curve representing the loss in body weight is an equilateral hyperbola. The several curves which I plotted on the basis of my own experiments as well as those of others (Springer, salamanders; von Linden, butterflies; Lasarev, guinea pigs) all coincide more or less with the curve of Falck. To elucidate this point further Avrorov's data on fasting dogs were plotted and analyzed mathematically. These data are particularly valuable since the weighings were made accurately to one gram and always at the same hour of the day. Besides, the dogs were in a calorimeter throughout the entire fast (23 out of every 24 hours) which, of course, insures the greatest uniformity of external conditions. (See Fig. 3)

The curve showing the daily change in weight of Avrorov's dog was made at my request by Dr. Hecht, who gives it the following interpretation: "The exact form of the curve is made evident by plotting the logarithm instead of the weight itself. The resulting graph, as shown in the figure, is a straight line. This means that the weight is a decreasing exponential function of the time, or

$$W_1 = W_0 . e^{-t} \qquad (1)$$

"The differential of this equation says that

$$-\frac{d\,W_1}{dt} = k.\,W_0 \qquad (2),$$

which means that the rate of decrease of the weight is proportional to the weight at that instant. If W_0 is the initial weight,

[1] A premortal rise in the loss of weight was also observed by Slovtzov in his study of May beetles but in other insects with which he experimented the curve, after an initial abrupt fall, declines gradually towards the abscissa.

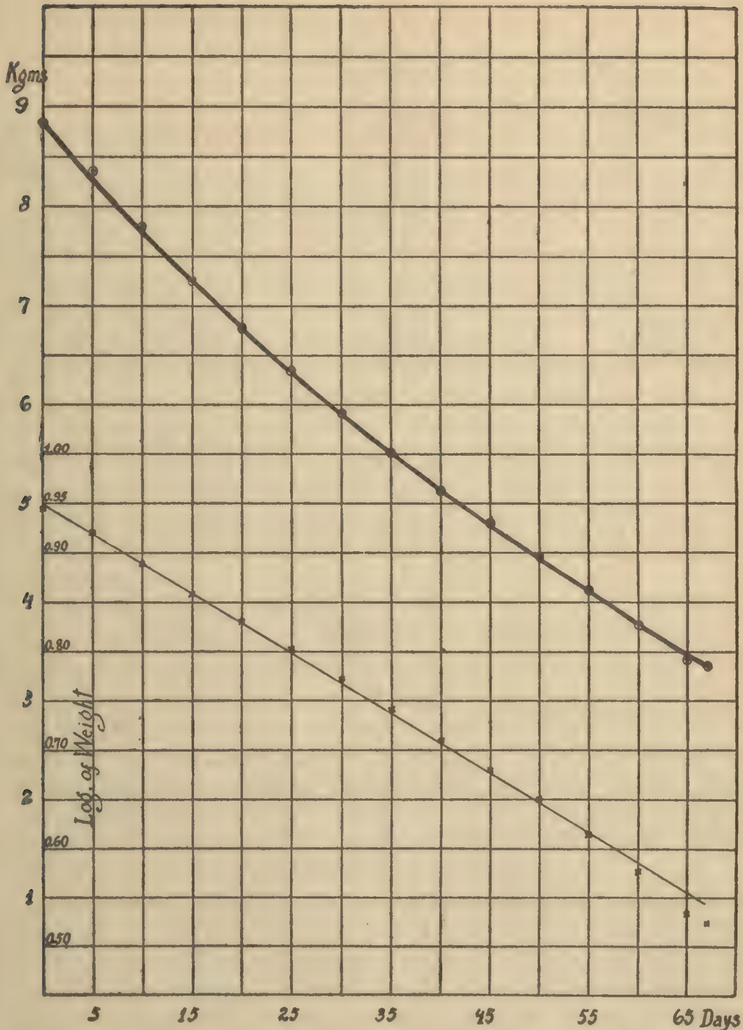

FIGURE 3.—Curve showing the changes in the body weight of a dog fasting 65 days. (Based on Avrorov's data.)

W_1 the weight at the time t, then the integrated form of the equation (2) states that

$$k = \frac{1}{t} \cdot \log \frac{W_1}{W_0} \qquad (3)$$

from which the theoretical value of the weight at any time may be calculated.

"It is apparent from the equation and from the agreement of the data with it that the curve is not one due to any conic section (i.e., hyperbola or parabola)."

Lang plotted the weight curves of Succi during his various fasts, also of Luciani's, Avrorov's, and Hawk's dogs which starved for different lengths of time (see Benedict, '15). His conclusion is that the curves betray no simple mathematical relationship. This is not at all surprising when one considers that the loss of body weight is not a simple process but the resultant of many processes. Ideal conditions are difficult to secure, and in this respect Avrorov's data are quite exceptional not only because of the remarkable uniformity of the environment during the fast, but also because the dogs were deprived of both food and water.

The loss of body weight which some of the more prominent professional fasters have sustained in the course of inanition shows that in no known instance has the fasting in man been carried to a point where, according to the general experience, his life has been placed in jeopardy. In the composite table on page 90 the total loss in weight is recorded, which these professionals have suffered in fasts varying from two to nearly six weeks in per cents of their initial weight. As these observations have been carefully supervised by scientific men the results may be regarded as absolutely reliable.

The greatest loss is usually suffered during the first day of the fast. The total loss, as will be seen from the tabulated data, is far below the limit which is considered dangerous for all other animals. Even after 40 days of fasting Succi lost only 25.3 per cent. His health had not been impaired by this experiment, and the fast could have been safely continued at least another week. Levanzin who in his 31-day fast lost about 22 per cent was in such excellent state of health that he discontinued the fast very reluctantly.

The study of the loss in body weight during inanition affords

TABLE I

Subject	Kozawa	Beauté	Schenk	Succi*							Jacques	Levanzin	Average Loss
Initial Weight Kilograms	50.7	65.8	56.4	63.5	65.2	71.7	63.5	63.0	61.0	55.9	62.3	60.5	
Duration of Fast													
14 days	13.3	11.9	13.3	12.9	10.6	11.1	13.3	15.7	12.6	12.7	11.3	12.4	12.59
16 "			14.4	13.1	11.2	12.1	14.2	16.3	13.8	13.8	11.8	13.8	13.45
20 "				16.7	13.2	13.7	16.6	18.1	16.6	16.1	13.0	16.0	15.67
29 "							20.3	21.8	20.9	20.6	16.4	20.7	20.11
30 "								22.6	21.4	20.8	16.6	21.4	20.56
31 "										21.0		21.9	21.45
40 "										25.3			25.30

*Succi's successive fasts took place at Naples, Rome, Zurich, Florence, Paris, Milan and London.

one of the best confirmations of Richet's law in comparative physiology, namely, that the intensity of all vital functions depends directly upon the size of the organism. The loss in weight is greater the smaller the animal, and this rule holds good not only for representatives of different groups but also of those belonging to the same species. This is well illustrated by the following data:

Animal	*Author*	*Initial Wt. in Kgms.*	*Loss per Kg. and per Hour*
Horse	Colin	405.0	0.28
Dog	Falck	21.0	0.36
Dog	Luciani e Bufalini	17.0	0.43
Dog	Falck	8.9	0.84
Cat	Colin	5.8	0.43
Cat	Bidder u. Schmidt	2.5	1.20
Rabbit	Rubner	2.1	1.70
Guinea pig	Chossat	0.55	2.30
Chicken	Kuckein	1.90	1.65
Pigeons	Chossat	0.35	1.73

This general law also applies to cold-blooded animals where the long duration of the fast makes up for the slow rate of decline. In the case of fasting salamanders I found that after 125 days of inanition an animal weighing 3.137 grams lost 37.1 per cent while another specimen weighing only 1.991 grams lost 43.9 per cent of its initial weight.

Coco-Pisano found that the loss in weight of the lizard *Gondylus ocellatus* follows the same course, namely, the total loss as well as the loss per hour of the fast being greater the smaller the animal. Arranging the results of his experiments with forty-nine lizards according to the average initial weight, four groups are readily distinguished:

Group	*Number of Lizards*	*Initial Weight in Gms. (Aver.)*	*Per Cent of Loss*		*Duration of Fast in Hours*
			Total	*Per Hour*	
1.	14	10.54	18.90	0.038	497
2.	22	21.54	17.43	0.034	507
3.	9	37.00	12.47	0.024	512
4.	4	51.02	10.08	0.019	518

Arranging the same data according to the average percentage loss, the inverse relation between the loss of body weight and the initial size of the fasting animal is even more striking.

Group	*Number of Lizards*	*Loss in Wt.* (%)	*Initial Wt.* (*Aver.*)	*Loss in Wt.* (*Per Hour*)	*Duration of Life in Hours*
1.	3	8.27	44.54	0.0161	509
2.	16	11.86	30.84	0.0249	518
3.	18	16.99	20.31	0.0398	481
4.	6	22.36	14.33	0.0404	553
5.	5	27.70	12.84	0.0537	515

Comparing the results presented in these two tables it is obvious that inanition is endured longer by the larger animals which probably depends upon the slower rate of loss of body weight. There is, however, no direct relation between the duration of the inanition and the maximum loss occasioned by it. It is important to bear this fact in mind, because the length of inanition is generally subject to much greater fluctuations than the total loss in weight sustained through fasting, especially among the higher forms, and therefore no general conclusion can be drawn as to the duration of the fast.

We cannot agree with Richet's opinion that the inverse relation between loss in body weight and the initial weight of an animal depends in the last analysis upon the extent of the heat dissipating body surface which, thus, is assumed to control the expenditure of energy and consequently the various organic functions. It is well to remember that not only the loss in weight, but the gain in weight during growth also obeys this law of inverse relation, as was demonstrated by Morgan for salamanders, the smaller animals growing more rapidly than the larger ones. In the regeneration of missing parts of worms I had occasion to point out that the replacement is more rapid the smaller the initial size of the regenerating piece. It is clear that the difference in both constructive and destructive processes could not be explained on the basis of a difference in the extent of the heat dissipating surface. Furthermore, this law operates among warm-blooded and cold-blooded animals alike.

The resistance of the organism to the deprivation of food, i.e., the duration of the fast until death, varies greatly. In man it may be assumed to vary from 17 to 76 days. In the dog, which has been the principal subject of inanition studies, this period is known to vary within still wider limits, from 21 to 117 days. Notwithstanding this large variation in the power of resistance to inanition, the duration is in a more or less direct

relation to the daily loss of weight sustained by the organism. The latter depends on certain known factors as, for instance, on the initial size of the organism. Large animals endure, therefore, the fast much longer than smaller ones, as will be seen from the following tabulation of the *average* length of survival of representatives from different animal groups:

Man	40 days
Dog	38 "
Cat	20 "
Rabbit	15 "
Guinea pig	8 "
Rat	2 to 3 "

For the same species it is undoubtedly true that the length of life under starvation generally depends upon the quantity of fat present in the organism at the start. This is shown in the following table in which the animals are arranged in the order of their initial fat content:

Investigator	*Animal*	*Body Wt. in Kgms.*	*Fat Content in %*		*Loss in Wt. %*	*Duration of Fast Before Death*
			Initial	*Final*		
Schimanski ...	Fowl	1.95	26	5	42	35 days
Kuckein	Fowl	1.00	9.1	0.7	39	12
"	Fowl	1.89	2.7	0.7	34	9
Rubner	Rabbit	1.51	7.1	0.4	49	19
"	Rabbit	2.34	6.3	0.5	41	19
"	Rabbit	2.99	2.3	0.3	32	9
Kaufman	Rabbit	2.08	2.3	0.4	35	8

The age of the animal subjected to inanition is also an important factor in determining its duration; young animals, being also of small size, succumb more rapidly and with greater daily losses than old animals. Arranging Falck's data on dogs, Chossat's on pigeons, and Dehon's on kittens according to the age of the animals, we obtain an interesting series tabulated on page 94.

The temperature of the environment exerts a strong influence upon the rate which the loss in body weight proceeds. In this respect, however, there is a striking difference in the behavior of cold-blooded and warm-blooded animals. It is a well-known fact that the fasting organism is exceedingly sensitive to cold which, of course, necessitates a more vigorous combustion of its reserves, and thus causing their quicker exhaustion. A high temperature, therefore, tends to conserve the energy of the fasting

Species	*Age*	*Initial Wt. (Grms.)*	*Duration of Fast*	*Daily Loss (%)*
Dog	18 hours	313	3.1 day	8.6
	14 days	1004	13.9 "	4.8
	1 year	8880	23.2 "	2.7
	Many years	21210	60.3 "	1.1
Pigeon	Young	110.4	3.1 "	8.1
	Medium	143.6	6.1 "	5.9
	Adult	189.7	13.4 "	3.5
Kitten	3 weeks	380	4 "	
	5 weeks	523	5 "	
	11 weeks	870	9 "	
	17 weeks	1140	8 "	

organism and to prolong its life. The condition is quite different in the case of cold-blooded animals, whose metabolic activity is regulated by the external temperature directly. In these animals a rise in temperature causes an increased rate of combustion and, consequently, a more rapid destruction of the reserves, while a lowering of the temperature, diminishing the oxidative processes, also reduces the daily loss in weight.

According to Aducco, darkness exercises a conserving influence on starving animals. Pigeons kept in the light endured privation of nourishment only two-thirds as long as other birds which were kept in the dark. The effect of the light, however, is entirely different from that of temperature. The effect is an indirect one, the pigeons being naturally less active in the dark than in the light.

Manca and Casella experimenting with lower organisms could find no evidence that light in any way affected the course of inanition.

We have considered so far the question of the total loss in body weight. How is this sustained loss distributed among the various tissues and organs of the organism? Voit compared the weight of different parts of a cat which died of inanition with those of another similar cat which served as a control. He found that the largest relative loss was borne by the fat depôt of the body, which was reduced to only about three per cent of its original mass. The liver lost 54, the muscles 31, the blood 27, the skin 21, the intestine 18 the bones 14, the nervous system about 3 per cent of its weight.

These results correspond well with those which Chossat found

for the pigeon. The difference between the results of these two investigators lies chiefly in the fact that according to Voit the heart suffers practically no loss, while Chossat finds a loss of over 40 per cent. Voit's findings, however, are not corroborated by other investigations which show that the weight of the heart usually diminishes considerably.

The most thorough investigation on the distribution of the loss in weight among the separate parts of the body has been made by Lasarev. The change in weight of the various organs bears no relation to the total loss of the fasting organism. In the initial stages of the inanition the greatest loss is sustained by organs and tissues which serve as storage places of nutritive material; also by such organs as the spleen which consists primarily of lymphoid, more or less mobile elements. The accompanying table gives the changes in weight (average) of the different organs of guinea pigs as their body weight decreased 10, 20, 30 and over 30 per cent.

An examination of the following table shows that after a loss of 10 per cent from the initial weight, which occurs practically after one day of fasting, the relative diminution of the organs follows this order: liver 17.98, muscles 7.28, heart 4.84 and pancreas 3.33 per cent of their original weight. The other organs remained unchanged or showed even a small gain over the normal. During the next two days of inanition, the total loss in weight having reached 20 per cent, the very appreciable diminution in weight of the skin, stomach, intestine and spleen is significant. The loss in weight of the liver, unquestionably associated with the depletion of its store of glycogen, which was large during the first day, continues now at a much slower rate until the store is completely exhausted. In the meantime the large loss now being sustained by the muscles, skin as well as the intestine suggests that the fat of which these organs are the chief depôts, is now lavishly drawn upon. The rather abrupt diminution in the spleen which occurs within the first two or three days of inanition and the fact that it changes very little during the subsequent course of the fast, leads one to believe that it is due to an emigration of leucocytes (a phenomenon the significance of which will be discussed in a later chapter) into the tissues which have become unduly exposed to bacterial invasion because of an increased permeability.

It is interesting to compare the relative losses in weight of

TABLE II

Average Loss of Weight in Per Cent	Average Wt. in Grams		Average Duration of Fast (Hrs.)	Percentage Change in Weight Compared to that of Normal Guinea Pig												
	Initial	Final		Lungs	Heart	Liver	Spleen	Kidneys	Pancreas	Stomach	Intestine	Skin	Spinal Cord	Brain	Femur	Muscles of Thigh
10	584	525	30.4	+0.93	−4.84	−17.98	0	+1.80	−3.33	+1.91	+0.49	−1.97	+1.05	−1.51	+2.13	−7.28
20	587	469	70.0	+0.31	−9.14	−23.51	−31.25	−2.55	−5.33	−6.49	−10.17	−8.17	−6.82	−3.02	+2.13	−14.93
30	580	405	121.4	−0.62	−20.97	−30.98	−37.05	−10.23	−24.67	−6.49	−10.54	−12.71	−6.82	−5.54	−3.55	−29.37
(30+)	580	374	164.2	−4.97	−33.33	−35.05	−43.75	−11.00	−39.33	−11.83	−25.80	−17.94	−6.82	−6.05	−2.81	−33.17

TABLE III

Percentage Loss in Weight of Various Organs

Organ	Pigeon			Rat	Guinea Pig	Rabbit	Cat		Dog		Man
	Chossat	*Lukjanov*	*McCarrison**	*Jackson*	*Lasarev*	*Weiske*	*Böthlingk*	*Sedlmair*	*Kumagawa*†	*Voit*	*Meyers*
Nervous System	1.9‡	4.02	2.4	B. 5.1 C. 0	6.45	...	17.3	14.0	22	B. 2.8 C. 7.2	+6.89
Bones	3.0‡	2.56	...	0.4	2.85	1.6	20.7	21.4	5	...	...
Skin	33.3	...	...	31.2	17.94	33.6	...	37.8	28	19.0	...
Muscles	42.3	...	...	30.9	33.17	41.9	64.2	67.3	42	43.1	...
Lungs	22.2	...	...	30.9	4.97	61.4	48.4	32.2	29	11.0	28.6
Heart	44.8	...	43.9	27.7	33.33	...	50.4	45.5	16	17.4	40.4
Stomach	39.7	...	27.2	57.0	11.83	33.1	36.5	57.0	32	24.7	51.5
Intestine	42.4	...	...		25.80	41.1	58.7			31.7	...
Kidneys	31.9	...	24.3	25.0	11.00	30.8	55.8	55.5	55	...	49.2
Liver	53.0	...	31.5	58.0	35.05	61.5	64.1	58.0	50	17.3	28.6
Pancreas	64.1	54.3	52.0	...	39.33	...	...	54.2	62	37.6	48.8
Spleen	71.4	73.3	70.3	51.0	43.75	70.6	65.5	74.2	57	21.2	18.4

* McCarrison's results are based on a study of 6 pigeons which have lost on an average over 40% of their body weight through inanition. The average weight of the fresh organs was compared with that of the same organs obtained from 35 control pigeons of both sexes. Apart from the data recorded in the table the following deserves special mention: The pituitary and the thyroid glands have lost 26.8 and 33.3% respectively; the thymus decreased by 89.7% and this should be considered in conjunction with the spleen which likewise sustained a large loss; the testicles and ovaries have lost 61.6 and 73.3% of their weight. Quite contrary to the behavior of the other internal organs the adrenal bodies increased in weight and in the starved pigeons they became 25.2% heavier than in the normal pigeons.

† On a fat-free basis.

‡ Loss of dry substance 9 and 17% respectively.

different organs in several animal groups. For this purpose Chossat's and Lukjanov's data on pigeons, Lasarev's on guinea pigs, etc., are compiled in the subjoined table (see page 97).

Two important facts are immediately revealed by glancing at the figures recorded in this table. In the first place, it is obvious that the proportional loss suffered by the organs of herbivorous animals is smaller at the time of death from starvation than that sustained by carnivorous animals or birds. This confirms the general belief that herbivorous animals are less resistant to inanition. Secondly, glancing down the vertical columns of data it can be seen that the nervous system and the bones usually bear a small loss. The actual loss may, however, be greater than the apparent one, since in both water replaces the fat present there originally. The skin and muscles, on the other hand, suffer a considerable loss. The percentage diminution of the organs of the thoracic cavity shows an appreciable advance over that of the former group, and the organs of the abdominal cavity reveal a still greater loss in weight.

Taking into consideration that these data have been compiled from widely scattered sources and that the methods employed by the various authors are not even comparable in many respects, their general agreement, in spite of a few exceptions, is striking and bears testimony to their intrinsic value.

Owing to unequal loss of weight sustained by the various organs of the body in inanition, the percentage of the total weight which these constitute is different in the starved organism than in the normal. This is of considerable importance as indicating that the unit of body weight may not only differ chemically but also morphologically in the fed and starved animal. In Table IV on page 99 I compiled practically all available data on this point; the importance of this information will become apparent when the physiology of inanition is discussed.

Recently McCarrison reported the interesting observation that in pigeons subjected to inanition the adrenals are generally much increased in weight. Vincent and Hollenberg, experimenting with pigeons, dogs and rats have confirmed this observation. After two weeks of inanition the adrenal bodies of the pigeons are hypertrophied to double the normal size. In the rat these authors found a similar hypertrophy of the thyroids. Thus in the normal rat the adrenals constitute 0.0167 to 0.0170 per cent of the total body weight, but after several days of starvation this

TABLE IV

PER CENT OF TOTAL BODY WEIGHT REPRESENTED BY DIFFERENT ORGANS IN THE NORMAL AND STARVED ORGANISM

Author	*Jackson*			*Weiske*		*Voit*		*Voit*		*Avrorov*	*Ohlmüller*		*Meyer-Boyd-Krieger*			
Animal	*Rat*			*Rabbit*		*Cat*		*Dog*			*Baby (56 days)*		*Human (Adult)*			
Organ	*Normal*	*Acute Inanition*	*Chronic Inanition*	*Normal*	*Starved*	*Normal*	*Starved*	*Normal*	*Starved**	*Starved†*	*Normal*	*Atrophic*	*Normal*	*Starved‡*	*Paupers*	*Chronic Malnutrition¶*
Brain	0.87	1.17	1.33	...	...	1.04	1.39	0.60	0.86	1.80	12.75	20.20	2.48	4.40	2.98	...
Spinal Cord	0.29	0.40	0.43	...	...	0.27	0.49	0.15	0.20	...			...	...	...	...
Eyes	0.13	0.19	0.20	...	...	0.27	0.51	0.18	0.20	0.23	0.19	0.23	...	...	...	...
Lungs	0.60	0.61	0.55	0.66	0.64	0.51	0.62	0.80	1.05	1.58	2.56	3.57	4.10	1.95	3.27	...
Heart	0.43	0.44	0.42	0.31	0.39	0.37	0.53	0.65	0.80	1.42	0.66	0.98	0.73	0.49	0.72	0.57
Stomach ..	6.00	3.40	3.50	1.49	1.62	3.80	4.65	1.22	1.36	1.05	4.42	5.89	0.38	0.31	0.35	...
Intestine ..				7.15	7.46			3.37	3.34	2.45			...	...	...	...
Pancreas ..	...	...	...	...	...	0.21	0.26	0.25	0.23	0.28	...	...	0.22	0.18	0.21	0.17
Spleen	0.27	0.21	0.31	0.09	0.04	0.28	0.14	(0.14)	0.16	0.14	0.49	0.28	0.48	0.15	0.44	0.24
Liver	4.50	3.10	4.00	3.75	2.59	2.96	2.03	2.18	2.66	3.70	3.41	4.38	5.30	2.53	3.59	2.99
Kidneys ..	0.95	0.96	1.00	0.58	0.69	0.81	0.89	?	0.45	0.79	0.78	1.05	0.73	0.60	0.70	0.60
Adrenals ..	0.017	0.022	0.026§	...	...	...	...	...	...	...	...	...	0.05	0.060	0.038	...
Testes	0.90	1.06	1.01	...	...	0.08	0.07	...	...	...	0.06	0.09	...	...	...	0.08
Muscles ...	45.00	47.50	43.00	46.55	46.41	45.36	46.89	39.70	33.30	34.40	25.82	23.61	...	...	...	...
Skeleton ..	10.00	15.00	16.40	6.77	11.31	12.67	16.22	15.50	26.80	26.50	16.99	25.53	...	...	...	...
Skin	18.00	19.10	17.80	14.62	16.77	13.94	16.45	11.00	11.50	15.50	31.16	12.21	...	...	...	...

* Loss 32%. † Starved till death. ‡ Dead from starvation; fasted 63 days, lost 40.7%.

§ Vincent and Hollenberg in their investigation of the relative weights of different organs in normal and starved rats found practically the same value for them as Jackson did for adrenals of the fed animals, namely, 0.018% of the total body weight, but in two rats which starved 10 to 12 days they found that the adrenals constituted 0.057 and 0.060% of the total weight.

¶ Marie Krieger examined the organs from a number of hospital patients who died in a state of emaciation with an average loss in body weight of over 41%. The patients represented 6 groups, (a) emaciation with no chronic organic disease (b) chronic diarrhea, (c) malignant tumors, (d) chronic infection, (e) tuberculosis, (f) old age. The largest proportional loss (48.4%) in weight was sustained by the group suffering from chronic diarrhea, and the least (35.8%) by the sixth group, old age. The adrenals in all the cachectic states were found 27% heavier except in the patients with diarrhea where this organ lost 9% of its weight.

increases to 0.057 to 0.060 per cent.. The thyroids likewise increase from 0.015 to 0.042 per cent of the total body weight. While the normal value of the adrenals is the same as that obtained by Jackson in his very extensive investigation of the inanition effect in the rat, the increase which he observed during acute fasting is very much less prominent (from 0.017 to 0.022 per cent).

McCarrison found that with the hypertrophy of the adrenal organ the amount of adrenalin is also increased. Vincent and Hollenberg's results on this point are not consistent, while Luksch, it may be recalled here, stated long ago that the chromaffine tissue of the adrenals is not affected by inanition.

To conclude this discussion we will compare the effect of physiological and experimental inanition. Valentin pointed out that the weight of the tissues of hibernating animals is only slightly affected as compared to the changes found in starving animals. Comparing Valentin's marmot which hibernated 163 days with Chossat's pigeons which starved about 10 days, it is noted that the pigeon consumes 40 times as much muscle substance, but only 11.3 times as much fat as the hibernating marmot. Besides it consumes 5 times more of the skin, 9 to 10 times more of the bones, 18.3 times more of the liver, etc. This comparison is very suggestive but of course must be regarded critically. If the necessary data were available, the comparison should be made for the hibernating marmot and the waking but starving marmot. This much, however, may be regarded as certain that in experimental inanition much more muscle substance is destroyed than in physiological inanition, when the organism exists chiefly on fat stored up in advance.

b. Changes in the Composition of the Organism

In the foregoing the changes in weight which take place in the various organs of the body were reviewed. We shall now carry the analysis a step further and inquire into the changes occasioned by prolonged starvation in the composition of the body and its different parts.

The fasting organism has a relatively higher per cent of water. This may be due either to a replacement of fat by water (bones), or to an actual retention occasioned by an accumulation of extractive substances (muscle). The concentration of tissue

juices is thus maintained more or less constant. Wherever a higher percentage of water is observed in a fasting tissue it means that the solid component has undergone greater reduction than its aqueous fraction.

Lukjanov made an extensive investigation on the distribution of water in the organism of starved pigeons. He showed that not all parts of the body are equally affected by inanition. Some organs retain a *status quo ante*, others (spleen, pancreas, liver) become slightly poorer in water content, while in the muscles and bones the water content increases considerably.

Böthlingk found that the per cent of water in the entire body increases during fasting. He experimented with mice whose initial weights were approximately the same. One set of mice fasted 75 hours and lost 33.25 per cent of their weight. In another experiment, lasting 158 hours, the animals lost 36.65 per cent of their initial weight. The bodies of both control and starved animals were analyzed, the results of the investigation being summarized below.

Experiment	*Loss of Body Weight*	*Per Cent of Total Weight*				*Per Cent of Dry Substance*		
		Water	*Nitrogen*	*Fat*	*Ash*	*Nitrogen*	*Fat*	*Ash*
Control	....	69.60	3.02	8.56	2.99	9.92	28.14	9.85
Fasting 75 hrs..	33.25%	70.71	3.58	2.58	4.32	12.24	8.80	14.76
Control	....	64.78	3.02	13.25	3.08	8.57	37.63	8.74
Fasting 158 hrs.	36.65%	72.22	3.39	2.27	4.31	12.20	8.18	15.51

The percentage of water, especially in the longer experiment shows a considerable increase over that found in the controls. It will be seen that the great diminution of the dry substance is due primarily to the using up of the fat, the proportion of this component diminishing from 13.25 to 2.27 per cent in the longer fast.

In a series of experiments on the common salamander, *Diemyctylus viridescens*, the author determined the change of the organism under the influence of starvation. Three groups of salamanders were deprived of nourishment for 51, 95 and 125 days respectively, and the entire animal analyzed. The results are given in the summary on the following page.

From this we see that the per cent of water does not increase continuously but, having increased at an early stage of inanition,

Per Cent	*Loss of Body Weight*	*Water*	*Dry Substance*	*Organic Matter*	*Inorganic Matter*
Control	...	74.9	25.1	21.7	3.4
Fasting 51 days....	20.8	76.3	23.7	19.7	4.0
" 95 days....	36.2	76.1	23.9	17.2	6.7
" 125 days....	49.0	76.3	23.7	16.3	7.4

remains practically constant. The starving organism subsists mainly on its organic substance, and therefore the ratio between inorganic and organic matter diminishes progressively, and from a normal ratio of 1:6.4 changes after 125 days of fasting to 1:2.2.

A similar increase in the proportion of the ash was observed by Schutz (from 16.6 to 28.6 per cent of dry substance), and by Lipschütz (from 11.8 to 23.3 per cent) in starving fish.

A comparison of the relative reduction suffered by the various components reveals some interesting facts. This is shown in figure 4 in which the change of each constituent during 125 days of inanition is represented by a separate curve. The quantity of each constituent in the normal salamander is taken as 100.

The loss of water is, therefore, proportional to the total loss of the body weight. The loss of organic substance is invariably greater than the percentage loss of the whole animal. The organic substance is lavishly expended, being lost at a greater rate than any other constituent, so that at the end of 95 days, when somewhat more than one-third of the body weight is lost, the organic substance has already diminished to about one-half of its initial quantity; and, lastly, after 125 days, when about one-half of the original body weight has been lost, the organic matter in the organism is reduced to about one-third. With regard to the inorganic constituent there is evidence of an absolute increase in quantity during inanition, though the results do not show much uniformity. Thus, after 95 days the quantity of ash is 27.2 and after 125 days only 8.2 per cent greater than at the beginning of the fast.

This observation of the increase in the quantity of inorganic material in fasting salamanders had no parallel in the literature at the time my paper was published. Since then, however, Lipschütz published similar results which he found in starving carps. These results are shown graphically in figure 5 (page 107).

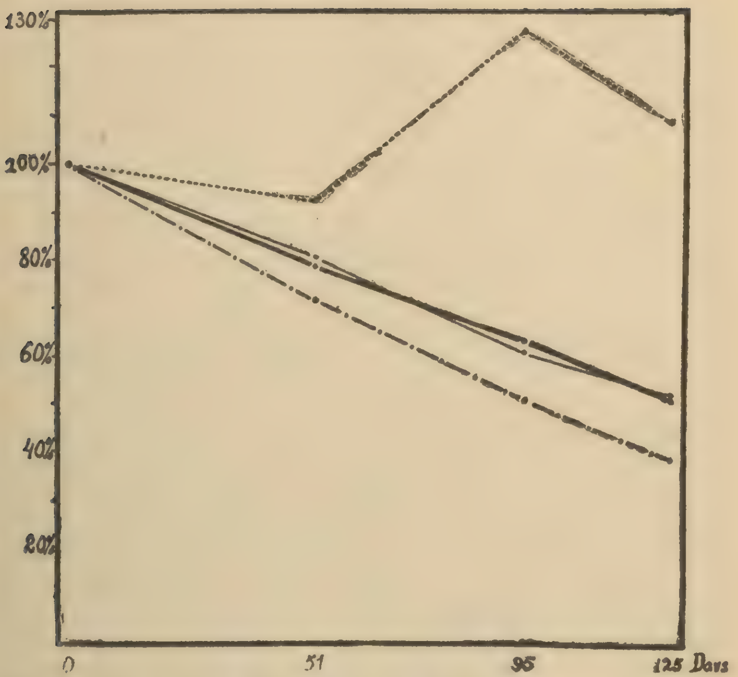

FIGURE 4.—This series of curves shows the simultaneous changes in body weight (heavy line); water content (light line); total organic matter (dash-and-dot line); ash content (dotted line) of the fresh water newt, *Diemyctylus viridescens*, after 51, 95 and 125 days of inanition. (Based on Morgulis' data.)

Two years later a similar observation was also recorded by Reuss and Weinland, who studied the effect of fasting on the chemical composition of eels (*Anguilla vulgaris*). In view of the interest which their investigation presents in this connection we shall discuss their analyses in detail.

The eels were divided into four lots, one (control) being at once analyzed, the second fed 50 days, while the other two lots were without food for a similar length of time at 18.8° and 12.5° C. respectively. The analyses included a study of the water, fat, nitrogen, glycogen and ash (also calcium). The changes which were found as compared with the first, or control lot are summed up in the table.

Condition	*Per Cent of Loss or Gain as Compared to Control*							
	Total Weight	*Water*	*Dry Substance*	*Fat*	*Nitrogen*	*Ash*	*$CaCO_3$*	*Glycogen*
Fed 50 days, 12.5° C....	+8.93	+4.6	+3.73	+40.0	+30.7	+60.3	+79.4	+17.6
Starved 50 days, 12.5° C.	−34.5	−29.7	−21.4	−20.4	−26.9	+18.3	+49.0	−82.4
Starved 50 days, 18.8° C.	−47.0	−49.0	−34.1	−43.2	−41.4	+23.6	+67.1	−100.0

It is evident from this that both lots of starved eels gained 18.3 and 23.6 per cent over the amount of ash which the control eels were found to contain. It is worth noting that the increase was much larger in the group kept at the higher temperature. This fact gains further significance in view of the circumstances that all other components of the organism have been used up more at the higher temperature, indicating a more active metabolism. The greater absorption of inorganic matter seems to stand in direct relation to this.

The gain in ash content in starving eels obviously depends on a retention of calcium as the composition of the fat-free substance in the different conditions shows:

Condition	*100 Parts Fat-Free Substance Contain*		
	Nitrogen	*Ash*	*CaO*
Control	15.45	14.44	4.46
Fed at 12.5° C	14.75	16.91	5.86
Starved at 12.5° C	14.39	21.79	8.47
Starved at 18.8° C	13.42	26.48	11.04

In starving flounders the author also observed a larger water content than in normal ones. The percentage of water in the

latter was 80.25 (young animals), but in two flounders, which fasted 28 days each, the percentage of water was 83.29 and 83.64 respectively. In one of these flounders, which lost 24.4 per cent of its weight the quantity of water diminished 31.21, while that of the fat and protein diminished 89 and 48 per cent respectively. Thus the preponderating loss is borne by the fat and protein, i.e., the organic substance of the organism. The loss sustained by the water moiety is more or less parallel to that of the entire body.

Lipschütz's results on fasting eels, recorded in the subjoined table, are of similar character. The eels were kept in aquaria without food for six weeks.

Percentage Composition of Eels	*Water %*	*Dry Substance %*	*100 Parts Dry Substance Contain*					
			Ash	*Nitrogenous Extractives*	*Protein*	*Fat*	*N-free Subst.*	*Carbohydrate*
Before fast..	79.4*	20.6	11.8	13.2	54.0	6.6	11.2	3.2
After fast...	81.3†	18.7	23.3	15.5	50.3	3.1	7.7	0.1

* 80.5% on a fat-free basis.
† 81.8% on a fat free basis.

The point of particular interest here is the fact that the percentage of the nitrogenous extractives increased while that of the protein decreased. The great diminution of the fat and the almost complete disappearance of the carbohydrates will also be noted.

The changes in the composition of the organism of animals lower in the scale follows the same general lines. Fasting lobsters show only a slight change in their gross weight, because, as I have shown, the actual loss is masked by an imbibition of water. Normal lobsters contain on the average 67.33 per cent of water, but in starved lobsters the proportion of water rises to 78.63. This increase by more than 11 per cent must be regarded as a unique occurrence.

The percentage composition of the dry matter of five normal and five starved lobsters (eight weeks) is given on page 109.

The dry matter of the starved lobsters is made up of practically equal parts of organic and inorganic substance, while in the normal lobster the organic matter is 64.3 per cent of the dry substance. About four-fifths of the inorganic substance is non-volatile, which is more than that found in normal lobsters, this

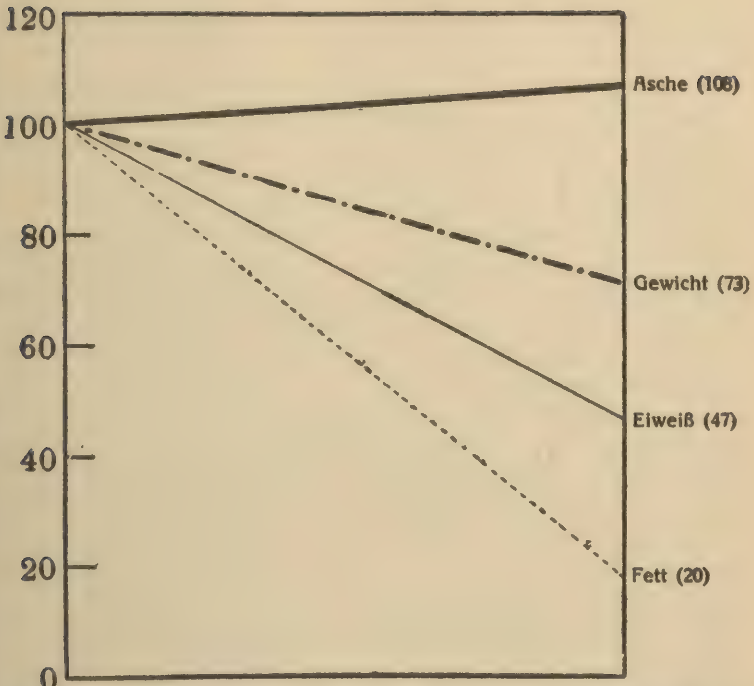

FIGURE 5.—Graphic representation of the relative changes in the weight of the whole body and of the different components of the organism of starved carps. (After A. Lipschütz.)

Condition of Lobster	Organic Matter	Inorganic Matter	Non-volatile Inorganic Matter	Glycogen	Extractives			Total Nitrogen	Protein (Non-extracted nitrogen x 6.25)	Undetermined
					Ether	Alcohol	Water			
Normal	64.305	35.695	27.409	0.494	2.919	5.605	10.528	6.636	31.544	13.215
Fasting (56 days)	50.370	49.630	49.817	....	0.238	1.691	5.767	4.475	22.425	20.249

being apparently due to a predominant loss of chlorides and carbonates. The water, ether and alcohol extractives show likewise a marked diminution, the quantity of ether-soluble substances being reduced to less than one-twelfth of the normal content.

Slovtzov made an interesting study of the composition of several insects in a normal and starved condition. May beetles, according to his findings, survive complete inanition about three weeks, and die having lost usually about 24 per cent of their weight. The extractives during the fast increase in absolute quantity, this increase amounting to 70 per cent. The water content diminished from 71 to 65 per cent, which must have been due to dessication, as no provision was made to moisten the air in the jars where the beetles were kept. The fact that the insects have survived only a comparatively small loss in weight strengthens my belief that the inanition here has been complicated by other factors, and that the excessive loss of water was a secondary phenomenon.[1]

The other insects used by Slovtzov for his experiments likewise died after losing only about one-fifth of their initial weight, sustaining at the same time a large reduction in their water content. This general diminution of the proportion of water places Slovtzov's observations in a class by themselves. It will be shown later that the resistance of the insects to inanition is inversely proportional to the accumulation of extractives. The excessive loss of water by desiccation favors such accumulation

[1] In another investigation on lizards, where the water content likewise diminished during fasting, Slovtzov thinks of the possibility of desiccation. He says in that connection: "Es wäre möglich daran zu denken, dass die grossen Wasserverluste den Tod durch Austrocknen früher hervorrufen, als die Tiere Korpervoräte verbrauchen." Recalculating his analytical data I find that the water of the organism has diminished by nearly 35 per cent of its original amount while the gross loss in body weight of the lizards was about 29 per cent. This furnishes positive evidence, therefore, of an actual desiccation of the tissues, and Slovtzov's experiments deal apparently with the combined effect of drying and inanition.

which poisons the organism even before inanition can exert its full influence. In this connection it may be pointed out that butterflies, which von Linden subjected to inanition, have usually succumbed after losing one-half or more of their original weight.

Slovtzov's investigation of the distribution of phosphorus and nitrogen in the organism of normal and starved beetles is of great significance, as may be appreciated from the examination of the summary of his results.

SUMMARY OF THE RESULTS OF

	Phosphorus Pentoxide			
	Total	*Alcohol-Ether Extract*	*Water Extract*	*From Nucleins*
1000 normal beetles	4.90	1.05	2.09	1.76
1000 starved beetles	3.55	0.19	2.90	0.46
Absolute loss or gain	—1.35	—0.86	+0.81	—1.30
Per cent of loss or gain ...	—27.6	—81.9	+34.9	—73.9

A consideration of the changes in the phosphorus shows very clearly that with the disintegration of phosphatids and proteins their phosphorus (diminished 81.9 and 73.9%) is transformed into inorganic phosphorus as is shown by the increase of that constituent (+ 34.9%). With regard to the nitrogen it is also very evident that upon the oxidation of the protein molecule a part of it becomes incorporated in the water-soluble extractive nitrogen. This agrees fully with what Lipschütz found in the fasting eel, viz., that the nitrogenous extractives increase in proportion to the total dry substance.

A comparison of Slovtzov's data on insects leaves no room for doubt that the resistance to inanition is related to the extent to which extractives accumulate in the organism.

Insect	*May Beetle*	*Dragon-fly*	*Humble-bee*
Change in water content...	—8.45%	—10.63%	—17.40%
Change in extractives...... (alcohol and water).....	+70.4%	+155.0% +88.9%	+89.5% +188.5%
Duration of fast..........	21 days	2.5-3.5 days	1-2 days

These data demonstrate that the desiccation of the insects runs parallel to the increased content of the water and alcohol-

soluble extractives and that both factors apparently conspire to shorten the insects' resistance to inanition.

It is interesting to note that the extracted substances obtained from muscle tissue increase in quantity during inanition. Valuable information on the composition of fish is given by Lichtenfelt, who finds that in inanition the muscles become not only richer in water but in extractives as well.

As far back as 1879 Demant showed that the creatine-creatinine

Slovtzov's Investigation

Nitrogen					
Total	*Alcohol-Ether Extract*	*Water Extract*	*Chitin*	*Protein*	*Ammonia*
37.46 30.93	1.52 0.62	4.72 6.97	2.42 2.49	26.77 21.57	1.64 1.48
—6.53 —17.43	—0.90 —59.1	+2.25 +47.6	+0.07 +2.80	—5.20 —19.4	—0.16 —9.8

content of the muscles of fasting pigeons is nearly twice as large as that of the normal birds. Hypoxanthin is present in variable quantities (0.028 to 0.060% of the dry substance) in the pectoral muscles of starving pigeons though it is absent from the muscles of normal birds. The lactic acid, on the contrary, is diminished possibly owing to the exhaustion of the glycogen.

Buglia and Constantino with the formol titration method demonstrated an increase in the amino acid nitrogen in the muscle of starving dogs. Their results are briefly summed up in the table.

Condition of Dog	*Loss of Weight*	*Grams Nitrogen in Dry Muscle*		
		Total	*Extracted N.*	*Amino Acid N.*
Control	...	13.98	1.63	0.34
Fasting 20 d.	—19%	14.86	1.75	0.45
Fasting 25 d.	—29.6%	14.01	1.72	0.43
Fasting 16 d.	—36.4%	14.49	1.82	0.43

The authors think that this increase is due to the failure of the ultimate products of protein hydrolysis to become oxidized. Van Slyke and Meyer, who likewise found the amino acid con-

tent of the muscles of dogs increased upon fasting, are inclined to attribute this to autolysis of fasting tissues.

Mendel and Rose have shown recently that there is an increase in the muscular creatinine during fasting. Their analyses are so interesting that their presentation in a modified tabulation will be valuable. In the case of the rabbits the composition of all muscles of the back and hind legs was studied; in the case of the hens, only that of the pectoral muscles.

Condition of Animal	*Loss in Weight %*	*Duration of Fast in Days*	*Muscle Analysis—Percentage*				
			Fat %	*Ash %*	*Water %*	*% Creatinine*	
						In Moist Muscle	*In Water-, Fat-, and Ash Free Muscle*
Control rabbits (3)	...	...	0.70	1.19	75.42	0.484	2.15
Starved rabbits (2)	25.3	9	0.485	1.19	77.50	0.570	2.58
Starved " (3)	35.6	14.3	0.467	1.11	79.24	0.595	3.11
Starved " (4)	44.8	16.5	0.390	1.12	79.48	0.554	2.92
Control hens (2)..	...	...	....	...	73.03	0.413	1.53
Starved hens (3)..	19.0	14	....	...	73.41	0.459	1.73
Starved hens (2)..	32.1	18	....	...	76.56	0.407	1.74

Horodynski, Salaskin and Salkowski found a small increase in the ammonia content of the muscle substance of starving dogs (from 12.94 mg. per 100 gms. of muscle to 14.36 mg. in the case of fasting dogs).

Tarozzi studied the effect of inanition on phosphocarnic acid, a complicated substance present in meat extracts and regarded by Sigfried as a nucleon. Tarozzi compared the phosphocarnic acid content of muscles of three normal dogs with that of three starving dogs (lost 10.28 and 45% respectively), and found both an absolute and relative increase in the starved animals.

The generally observed increase in the amount of extractive substance is probably due to the sluggishness of the lymph circulation through the tissues.

Considerable chemical changes are observed in the muscles during inanition. Referring to the results of Mendel and Rose, we find that the percentage of water in the muscles of both the rabbit and the hen increases progressively with the fast. Thus, in the case of the rabbit:

Condition	*Loss in Weight*	*Percentage of Water*
Control	.... .	75.42
Starved	25.3%	77.50
"	35.6%	79.24
"	44.8%	79.48

C. W. Green observed that the muscle substance of the Pacific salmon becomes likewise richer in water (on a fat-free basis) with the progress of the fast which these fish undergo during their sojourn in the fresh water streams. The condition is, of course, a great deal more complicated in this case than in animals starving under experimental circumstances, because the salmon performs a huge amount of work in its upstream migration and the simultaneous development of the gonads is an additional drain upon the reserves of the muscle tissue. The percentage of fat gradually diminishes, in both rabbit and salmon, and the percentage of ash remains practically constant during the fast.

Analyses of muscles of salmon taken at three different stations along the Columbia River—at the mouth, mid-course, and 700 miles upstream—show the following results:

Water	74.7%	77.0%	81.5%
Protein	20.2%	18.2%	14.0%

Two important facts need be pointed out here: First, the very large increase in the percentage of water (this was determined on a fat-free basis, and considering that the fat content at the mouth of the stream may be as great as 20 to 30% while upstream less than 3%, it is clear that the change is much more striking than in the rabbit's muscle); secondly, the marked and progressive decrease in the proportion of protein, which as will be shown subsequently does not occur in ordinary fasting. Both these occurrences are correlated to the extensive dissolution of the proteins. This excessive destruction of muscular substance to furnish building material for the growing gonads and energy for the work of migration liberates much water which is retained by the tissues.

A perusal of Weiske's analyses of the muscle substance of fasting rabbits gives a still better idea of the nature of the changes that take place. The parallel two columns show the percentage composition of a normal rabbit's muscles and the average composition of muscles from three starved rabbits which lost 30.4 per cent of their weight.

	Normal	*Starved*
Dry substance	24.45%	20.97%
Water	75.55%	79.03%
Fat	4.03%	0.69%
Nitrogen	3.04%	3.09%
Protein	19.00%	19.30%

From this series we can see that the percentage of fat has diminished to about one-sixth, that of nitrogen has somewhat increased, while the water content became about 3.5% greater. Calculated on a fat-free basis, however, the percentage of water remains practically the same (79.85 and 79.72% respectively).

A comparison of the percentages alone fails to convey a clear idea of the actual alterations which take place. I recalculated Weiske's results with the object of bringing out more definitely the changes. In these calculations it is assumed that the starved rabbits had the same composition as the control when the fast began. On this basis the following changes are found:

	Control Rabbits	*Starved Rabbits (Three)*			
		Weight in Grams			
	Weight in Grams	*Before Fast*	*After Fast*	*Difference*	*Difference in Per Cent*
Body weight	2220.0	2437.0	1477.0	—960.0	—39.40
Weight of muscles..	1025.0	1135.2	687.3	—447.9	—39.45
Dry substance	251.7	277.6	144.2	—133.4	—48.06
Water	773.4	857.6	543.1	—314.5	—36.67
Fat	41.3	45.8	4.7	—41.0	—89.86
Nitrogen	31.2	34.5	21.2	—13.3	—38.48
Protein	194.6	215.7	132.7	—83.0	—38.48

We thus discover that the muscle mass diminishes in the same ratio as the entire body (39.4%); that the loss of protein is also practically in the same ratio (38.5%); that nearly nine-tenths of the fat is exhausted, and, finally, that the dry matter diminishes relatively one-third more than the water. The higher percentage of water in the muscle of starved animals is, therefore, not an indication of an increased content of water but more correctly of a more rapid diminution of the solids.

Pflueger has shown that at any rate in a dog which fasted 28 days there is still a considerable amount of glycogen present

in the tissues. As much as 0.16 per cent was found in the muscles. C. W. Greene studied the carbohydrates of the king salmon tissues during their migratory period. As is well known, the salmon are in a state of inanition during that period which sometimes extends over several months. The glycogen is not absent from the tissues during that period, though it seems to disappear very quickly from the muscles. In the liver the glycogen drops to a low level but does not entirely disappear. On the contrary, there appears to be a synthesis of glycogen in the ovaries which develop during the migratory period and their glycogen content remains practically constant at about 0.1 per cent pointing definitely to a uniform formation and accumulation of this substance in the growing egg-cells.

The composition of the muscle ash also presents considerable interest when the data are studied from the same point of view as was applied in the consideration of the muscle composition.

The percentage of ash remains unchanged, but a comparison of the ash constituents at the beginning and at the close of a fast yields information which is much more significant. Weiske determined the calcium, sulfur and phosphorus in the muscles of rabbits. On the basis of the percentages which he gives in his paper (1896) I made the following computation:

	Control	*Starved Rabbits (Loss = 39.4%)*			
	Weight in Grams	*Weight in Grams*		*Difference*	
		Initial	*Final*	*Grams*	*Per Cent*
Ca	1.0937	1.2043	1.2920	+0.0877	+7.28
S	1.8719	2.0613	1.3613	—0.7000	—33.96
P	2.3136	2.5476	1.5198	—1.0278	—40.35

We can see from this that while both the sulfur and phosphorus of the fasting muscle diminish in about the same ratio as the protein, and, therefore, the entire muscle mass, the calcium behaves in a wholly different manner. It actually increases in amount so that after the fast there is 7.28 per cent more calcium in the muscle than there was in the beginning. This, of course, recalls the observation which Reuss and Weinland made on starving eels. In my own experiments on salamanders where it has been discovered for the first time that dur-

ing prolonged starvation the inorganic matter may increase in absolute amount, the different constituents of the ash were not analyzed, but it may likewise have been a case of calcium absorption by the tissues. Evidently there are some changes occasioned by inanition, possibly in the colloidal state of the protoplasm, which conduce to such an absorption and accumulation.

Investigating the modification in the composition of the entire organism of starving mice, Böhtlingk determined the sodium and potassium in the ash. Since these substances are present in the skeletal portion of the organism only in very negligible quantities, it is safe to assume that they were derived chiefly from the muscles which make up the bulk of the soft portion. The results are tabulated below.

Condition of Mouse	*Grams*		*Per Cent of Ash*		*Per Cent of Total Weight*	
	K_2O	*Na_2O*	*K_2O*	*Na_2O*	*K_2O*	*Na_2O*
Control (aver.)	0.0151	0.0260	2.252	3.878	0.068	0.117
Starved (aver.) ..... (—36.7%)	0.0138	0.0147	2.208	2.352	0.094	0.102

The percentage of potassium in the body as a whole (soft parts) increases during the fast, which shows that the potassium is not lost as rapidly as the other constituents of the organism. The percentage of sodium, on the contrary, diminishes. When we compare the absolute quantities of both sodium and potassium in the control mice and in the starved mice (their initial weights were the same) we find that the former actually diminishes by 43.5 per cent, the latter by only 8.4. In other words, sodium is lost in a greater proportion, while potassium in a much smaller proportion than the rest of the soft tissues. Sulfur and phosphorus, as was shown by their behavior in the muscles of starving rabbits, occupy apparently an intermediate position: the sulfur diminishing slower than the entire muscle mass while the phosphorus diminishes in practically the same ratio. We thus get a series: K, S, P, with a pronounced progressive tendency to be lost in inanition. It is probably not a mere accident that the reabsorbing power of the renal tubules diminishes along this series also, so that the greater or smaller loss of these elements stands in direct relation to the ability of the kidney to eliminate them.

The blood though less markedly affected than other tissues shows nevertheless certain definite changes in composition resulting from inanition. Popiel found that in starving rabbits the specific gravity of the blood changes (on the average) from 1045.4 to 1053.3. In the dog, however, he observed a very much less pronounced change (from 1048 to 1050.8). It should be mentioned, perhaps, that London using the same method (Hammerschlag's) found that the specific gravity of the blood of starved rabbits diminished. His results, however, are inconclusive owing to the fact that the blood volume increased from 4.79 to 4.98 per cent of the body weight, and the lowered specific gravity observed by London was probably due to a condition of hydremic plethora.

Certainly the freezing point determinations made cryoscopically on bloods of normal and starved animals indicate a condensation of the blood. Though the earlier experiments of Fano and Bottazzi on dogs show no regularity in this respect, the results of later experiments are more concurrent. Mayer recorded a change from — 0.60° to — 0.62° C. in a dog which lost 15 per cent in body weight. Tria working with both dogs and rabbits found that the freezing point depression changed on the average from — 0.61° to — 0.65° C. in fasting animals. Polanyi's experiments on dogs show even a greater change.

Normal	*Fasting*
—0.55° C.	—0.60° C. (14 days)
—0.607° C.	—0.640° C. (14 days) —0.729° C. (21 days)
—0.564° C.	—0.620° C. (14 days with water)

The evidence seems conclusive that the osmotic pressure of the blood serum increases (greater depression of freezing point) during inanition. The viscosity decreases (Tria, Polanyi) while the electrical conductivity shows a very slight rise (Tria). The former may perhaps be due to a diminution of the dry substance, particularly of its protein moiety, as was shown for the serum of fasting dogs by Polanyi.

Normal	*Starving*
8.62% protein	7.10% protein (14 days)
9.20% "	8.72% " (14 ") 7.50% " (21 ")
9.49% "	8.49% " (14 ")

The results of different investigators of the condition of the blood cannot be said to reveal much agreement. Robertson with the use of the refrectometer shows that the total protein content of the serum rises. Furthermore, in the rabbit, ox and horse starvation leads to an increase in proportion of albumin to globulin in the serum, while in the cat and dog starvation leads to an increase in proportion of globulin to albumin. This, however, is contradicted (for the rabbit, at any rate) by Hanson, who finds that the Globulin-Albumin quotient of the blood is not affected by prolonged fasting.

The increase in conductivity as well as the greater lowering of the freezing point of the serum of starving animals is doubtless associated with the higher per cent of ash:

	Normal Dog (Average)	*Starved Dogs*		
		(14 Days)	*(14 Days)*	*(21 Days)*
Total Ash ...	1.101%	1.320%	1.110%	1.121%
NaCl	0.744%	0.832%	0.780%	0.832%

The greater ash content of the serum is evidently due to the relatively higher proportion of the water-soluble salts (NaCl) since the water-insoluble component remains practically unchanged (Polanyi). It is well to point out in this connection that Bottazzi and Cappeli found in a dog which lost 31 per cent of its body weight in 24 days of fasting that the percentage of sodium of the erythrocytes diminished from 0.2896 to 0.2712, while that of potassium remained practically unaffected at from 0.0263 to 0.0258. The increase of the sodium salts in the ash of the serum may be, therefore, partly due to an actual migration of Na-ions from the cells into the plasma. Of course, the decrease of total solids which is principally at the cost of the serum proteins leaves the inorganic constituents in a larger proportion. In other words, the greater per cent of ash in the serum from starved animals results from the unequal rate at which the organic and inorganic fractions are being used up. This condition we already found to hold true with regard to the changes in the body composition in general.

That the higher per cent of ash does not indicate actually *more* ash than is present in normal blood, and that the absolute quantity of sodium and other soluble salts diminishes is best proven

by the fact that the blood alkalinity decreases during fasting. Thus, Tauszk found for the professional faster Succi that the alkalinity diminished from a normal level equivalent to 0.68 gm. NaOH per 100 c.c. blood to 0.18 gm. on the third day of fasting and remained with slight variations at that low level up to his thirtieth fast day.

Recent studies of Asada, who followed with the Van Slyke method the changes in the alkaline reserve of arterial blood of rabbits in various stages of starvation, furnish even more definite evidence of a diminishing alkalinity and progressive development of acidosis. His results, somewhat condensed, are presented below:

Condition of Rabbit	*Arterial Plasma Bicarbonate C.c. of* CO_2
Normal	
"	0.5495
"	0.5666
Fasting	
1 day	0.4938
2 "	0.5170
4 "	0.4096
6 "	0.4112
10 "	0.3423
13 "	0.3723
16 "	0.2720

It has been shown by a number of investigators that the fasting blood contains more fat. Thus Schultz extracted with ether the dry residue remaining after digesting the blood from both normal and starving rabbits. In two different sets of animals fasting four to five days an increase of 50 and 83 per cent in the blood fat was found. Likewise the blood of pigeons, which twelve hours after feeding contains on the average 0.6 per cent of fat, contained after five days of fasting 0.78, or 30 per cent more, and in a few instances Schultz found an increase of even 100 per cent over the normal fat content.

Green and Summers record a rise in blood fat content of 230 and 185 per cent respectively in starving puppies. These investigators were unable to produce any changes in the blood fat of adult dogs even by a prolonged fasting. The results bearing upon the lipemic condition of the blood in starvation are not uniform. Evidently the starvation lipemia depends upon a variety of

factors, and experiments are needed with more strictly controlled conditions before any conclusions can be drawn as to their significance.

It may be recalled here that Mottram believed to have demonstrated fatty infiltration in the liver of starved animals. In spite of his painstaking efforts and critical attitude to the data, it seems to me that he has not succeeded in proving his thesis beyond the mere fact of showing that already after 24 hours of fasting there appears in the liver cells visible fat. Inasmuch as the glycogen is almost completely consumed within the same time from the liver cells, a protein-fat colloidal system results which easily breaks up with the formation of free globules of fat because there is no glycogen present to stabilize the emulsion.[1]

It is possible that the lipemia of starvation is also the result of a change in the condition of the colloidal system.

The hyperglycemia of starvation may have its origin in the same fundamental alterations of the colloidal state of the protoplasm. At any rate, in starved cats which Lee, Scott and Morgulis investigated (unpublished results) the blood sugar was found to be permanently above the normal level. The blood sugar curve corresponding to the different losses in body weight show a fairly sharp rise reaching a maximum (0.133%) when the loss is between five and ten per cent, i.e., after 48 to 72 hours of fasting; the curve rapidly declines, then rises again to a second smaller peak (0.110%) when the loss in body weight is 20 to 25 per cent. The curve begins to fall off once more but even when the body weight loss is about 40 per cent the sugar content of the blood is still 0.085 per cent, which is considerably above the blood sugar level of normal cats (0.069%).

In experiments on fasting dogs which are now in progress Morgulis and Edwards[2] found that the amount of the sugar in the blood generally diminishes, but in the very advanced stage when the dogs have already lost about 40 per cent of their weight the blood sugar level rises rather abruptly. At this stage of the fast the blood sugar content may even exceed that found in the animal before the fast began. In none of the analyses so far performed has the sugar level diminished below 60 mgm. per 100 c.c. of blood. These results may be compared with the findings on

[1] D. M. Ervin, *Jour. Lab. and Clin. Med.*, 5, 147, 1919.
[2] Unpublished results.

the bloods of marine invertebrates reported by Morgulis. Studying the blood of arthropods it has been shown that in most of the animals investigated its composition undergoes very quick changes as soon as the animals are deprived of food. In the horse-shoe crab (*Limulus*) the sugar practically disappears when it has been in captivity for some time. In several other forms (lady crab, spider crab, the Tortugas crawfish) striking alterations have also been observed within two days of fasting. So far the lobster (*Homarus*) is the only arthropod examined in which these abrupt and quick changes in the composition of the blood did not appear.

The bones sustain only a slight loss in weight; owing to the replacement of the used up fat by water, the actual change in weight in the early stages of the fast are probably obscured. In the case of rabbits which lost 31, 40 and 43 per cent of their initial weight Weiske found that the weight of the entire skeleton (fresh) has shown an increase by 2.8 and 2.5 per cent respectively in the first two and a loss of only 1.6 per cent in the third rabbit.[1]

The dry substance of the bones in the three starved rabbits diminished 11.1, 8.7 and 16.5 per cent, which is additional proof that during inanition water replaces fat in the bones. Lazarev in his study of the different organs of starving guinea pigs (see previous chapter) also found that the skeleton becomes somewhat heavier in animals which lost even as much as 20 per cent in weight.

Gusmitta removed aseptically the right ulna and radius from a dog which after recovery was subjected to a forty-day fast (lost 41.3% in weight). The ulna and radius of the left limb were now also removed and analyzed. The bones from the right side served as a control. He found that the bones at the end of the fast were smaller in volume (decreased by 4.9 and 6.7 per cent), with a lower specific gravity and a greater number of pores. The only appreciable change in the chemical composition is the lower per cent of calcium carbonate in the bones after starvation.

[1] The values here quoted do not tally with those given by Weiske. His computation of the data is, however, erroneous as he simply compares the absolute quantities found for both the starved and the control rabbits. It hardly needs discussing that such a procedure is entirely wrong. We can only compare the quantities present in the same animal before and after the fast, using the percentage composition of the control animal to calculate the probable initial quantities in the starved animals. I recalculated his numerous data on this basis.

According to Sedlmair the loss is greater in the bones of the extremities than in the remaining bones of the body if the loss of the dry substance alone is considered. This is easily explained on the assumption that the loss is principally at the expense of fat. On a water- and fat-free basis the composition of all bones of the starving cats (Sedlmair) is almost the same as to the normal cats. Just on a dry basis the percentages of organic and inorganic constitutents of the bones increase during fasting.

Condition of Cat	*Dry Bones*				*Water- and Fat-Free Bones*		
	Fat	*Ash*	*Ossein*	*CaO*	*Ash*	*Ossein*	*CaO*
Normal	12.56	50.95	35.17	26.14	58.27	40.16	29.90
Starved							
Lost 50.6%.	2.34	56.55	40.22	29.68	57.90	41.18	30.39
Lost 54.6%.	4.11	55.46	38.68	29.20	57.84	40.34	30.45

Weiske analyzed bones and teeth of starving rabbits determining the proportion of the different inorganic elements. In the bones he found practically no difference in the percentage of organic substance or of the other constituents. In the teeth, however, a small but unmistakable change in the composition took place. This can be seen from the table below:

Constituent	*Control Rabbit*	*Starved Rabbits*		
		—35%	*—40%*	*43%*
Organic subst.	23.42%	21.80%	21.52%	22.09%
Ash	76.58	78.20	78.48	77.91
CaO	37.88	38.75	38.92	38.83
MgO	2.49	2.44	2.48	2.37
CO_2	0.77	0.99	1.10	1.45
P_2O_5	33.91	34.21	34.46	34.24

There is a marked diminution in the organic matter of the teeth of fasting rabbits. It is doubtful, however, that this is caused by an actual consumption of the organic material. The teeth of rabbits grow continuously and it is therefore probable that the diminution of the organic fraction is due to a deficiency in this building stuff.

It must also be noted that Wellmann compared the composi-

tion of skeletons of two normal rabbits with the skeletons of two others which died from starvation (average loss in weight 40.5%). The percentage of water in the skeletons from the two groups was 35.2 and 38.3 respectively. Unlike Weiske or Sedlmair, he found the organic substance of the bones also diminished as may be seen from the table giving the percentage composition of the dry and fat-free bones:

Rabbits	*Organic Matter*	*Ash*	*P*	*Ca*	*Mg*
Control ...	39.06	60.94	10.62	22.43	0.4709
Starved ...	37.45	62.55	10.93	22.64	0.4679

The change in the chemical composition of the bone-marrow is even very much more striking. Aron[1] states that in starved calves the marrow is reduced to a watery mass. Roger and Josué, whose morphological study of the bone-marrow in fasting will be discussed in the next chapter, found the following changes in the chemical make up of the marrow of starving rabbits.

Component	*Normal Rabbit*	*Starved Rabbits*			
		—19%	*—25.6%*	*—24.6%*	*—29.6%*
Water	31.9%	85.54%	78.10%	86.63%	82.24%
Fat	50.76	0.80	8.26	1.02	3.44
Soluble protein	0.77	4.06	4.32	3.56	3.23
Insol. protein..	2.76	4.97	4.91	3.39	3.48

In no other tissue do we find a similar condition. The fat is almost completely exhausted and the amount of water is practically tripled. But what merits especial attention is the enormous increase of the soluble protein moiety. It is this which gives to the marrow of starved organisms its peculiar gelatinous appearance.

The changes which inanition occasions in the composition of the body affect not only the individual enduring the deprivation of food, but also the offspring. This transmitted effect and all it may spell in misery for the next generation has a particularly great significance in its bearings upon social problems. The topic should therefore be approached with a breadth of view

[1] Ich habe die Markhöhle der Knochen an Inanition zugrunde gegangener Kälber mit einen ganz wässerigen Mark gesehen, das nur wenige Proz. Trockensubstanz und einige Zehntel Prozent Fett enthielt. Hans Aron, Handb. d. Biochemie, V. 2. p. 193.

and a confidence of fact as the far-reaching importance of the conclusions requires. At present, however, we are still at the very beginning of such an experimental investigation.

Ugriumov studied the composition of young rabbits born of males which were in various stages of inanition. Their offspring were compared with those produced by the same pair while the male was well nourished. The offspring of a starved rabbit, even if it lost only 12 per cent of its weight, show diminished vitality, and have so little stamina that they frequently die soon after birth. When the exhaustion of the male has progressed still further, the young are almost invariably still born. Normal litters contain four to seven young whose average weight is 41.18 grams. Litters from starved fathers contain usually four to five young with an average weight of 40.81 grams. The dry substance of such offspring contains less nitrogen than those from normal parents, also less calcium, sodium, and potassium. The amount of fat, on the other hand, is much greater, which Ugriumov regards as a pathological phenomenon, resulting from the low vitality of the young, and

TABLE V

Régime	*Weight of Litter (Grams)*	*Per Cent of Water*	*Per Cent of Dry Substance*			
			Nitrogen	*Fatty Acid*	P_2O_5	SO_3
RABBITS						
1. Full diet	183.90	79.35	9.43	17.02	4.13	1.54
2. 1/5 of requirement.	111.77	85.27	11.21	15.60	2.11	1.73
1. Full diet	186.70	82.39	10.94	16.09	4.44	1.36
2. 1/5 of requirement.	82.22	85.59	11.82	12.18	2.00	1.54
1. Full diet	381.50	80.59	10.87	19.71	4.61	1.29
" "	246.48	80.41	11.28	20.66	3.97	1.37
2. 1/5 of requirement.	263.96	84.88	11.80	18.26	4.29	1.50
1. Full diet	302.50	79.38	9.77	18.82	4.32	1.49
2. 1/10 of requirement	58.89	86.41	13.02	13.92	3.58	1.33
1. Full diet	203.95	80.13	8.98	17.54	4.92	1.83
2. 1/10 of requirement	58.24	88.46	11.90	13.86	5.25	1.68
3. 1/20 of requirement	44.45	88.42	11.89	14.45	...	...
DOG						
1. Full diet	788.0	76.61	11.15	19.63	4.50	1.72
2. 1/10 of requirement	833.5	81.53	12.46	17.08	4.93	2.42

compares this condition to the obesity running in some families afflicted with disease.

Rudolski studied this problem from a different viewpoint. In his experiments performed almost exclusively on rabbits (only one experiment on a dog) it was the female which was subjected to inanition during her pregnancy, the males having been well fed. The inanition, furthermore, was not complete, because under such circumstances the rabbits almost invariably give birth prematurely. The pregnant females were given an insufficient diet varying in quantity from one-fifth to one-twentieth of their normal requirement. In other words, the animals were chronically underfed. Under these circumstances abortions were not very frequent; the litters of young were much lighter in weight and their chemical composition was fundamentally altered.

It is evident from Table V that young animals born of underfed mothers show every indication of being themselves in a state of inanition. The invariably high percentage of water in their tissues and the low proportion of fat speak strongly for this assumption. The relatively high percentage of nitrogen in offspring from starved females as compared to that of the offspring born in a period of normal feeding reminds of a similar increase in the percentage of nitrogen in the fasting organism already pointed out. The sulfur, with few exceptions, is lower and the phosphorus is higher in offspring of well-fed animals.

CHAPTER II

CHEMICAL PHENOMENA IN INANITION

a. Metabolism of Matter and Energy

Deprived of food the organism must naturally subsist upon its own body substance and derive the energy necessary for maintaining its functional activity from such stores as are deposited in its tissues. Under the circumstances the metabolic processes are reduced to a minimum, first, because in the absence of digestive activity a certain amount of energy is being spared, and, secondly, because in prolonged inanition the organism tends to use economically its material resources. On this account the metabolism in fasting received much attention ever since the problem of nutrition has been subjected to scientific inquiry.

It is undoubtedly a fact that the different organs are competing vigorously for the available supplies of nutriment and energy, sharing to a greater or less degree in the total loss suffered by the fasting organism depending on the quantity of the material which they are able to acquire for their own sustenance. This competition does not go on between different systems of organs only, but between the various tissues of which these are made up, and even between the ultimate units of the organism—the cells themselves; furthermore, there is evidence to show that the different structural parts of the cell are unequally affected by the struggle for existence. Besides, as has been already shown in the foregoing, the different chemical components are metabolized at widely varying rates which results in a qualitative alteration of the composition of the organism.

Life is essentially a chemical process since the ultimate source of energy must be in the chemical transformations. These chemical phenomena, which in their totality constitute the metabolism of matter and energy and thus form the basis of life, must continue during inanition. The nature of the energy-yielding material furnished by the organism itself is essentially

different from that ordinarily derived from the food, and this difference sometimes exerts a strong influence upon the organism's metabolism. Thus, herbivorous animals, when made dependent upon their own accumulated nutrient supplies through fasting, are suddenly turned into carnivorous—subsisting now on material of animal origin—and this radical change manifests itself immediately in a greatly increased quantity of acid waste products of their metabolism. The fasting infant is another striking example of this sort, because it too is changed from a lactivorous to a carnivorous organism. A normally fed baby subsists chiefly on fat and carbohydrate, and only to a limited degree on protein which it utilizes principally for constructive purposes, the building up of its tissues and growth. In fasting, however, especially when the glycogen store has been nearly exhausted, the protein is being more and more metabolized for energy.

Another matter that needs to be considered is the fact that as glycogen is quickly used up with the onset of inanition, only traces remaining in the tissues, the organism subjected to protracted starvation becomes an essentially fat-protein system. Though we are still in the dark as to the effect which this change from a carbohydrate-fat-protein colloidal system to a predominantly fat-protein system may exert on the chemical processes in the organism, it will be seen later that certain phenomena can be traced to such alteration in the colloidal state of the protoplasm.

The oxidative power of the organism is believed to be diminished in inanition. Pugliese administered small quantities of phenol to dogs in a well nourished and in a starved condition, and studied the rate of oxidation. He found that in the fed dog 32 to 35.6 per cent of the phenol was oxidized and 64.5 to 68.1 per cent was eliminated through the urine as ethereal sulphates. The same dogs when fasting eliminated 82 to 85.3 per cent of the phenol in the urine while only 14.7 to 18 per cent of the administered quantity was oxidized.

1. *Synthetic Process in Inanition.*

It is erroneous to think that since tissue destruction predominates in inanition no synthetic processes occur at the same time. Thierfelder found glycuronic acid in the urine of starved rabbits and dogs to which he had administered chloralhydrate

or tertiary amyl alcohol. The quantities of glycuronic acid recovered were so large that even had the starved animals still contained as much glycogen as they possessed in the normal condition, this glycogen could not have sufficed to form all the glycuronic acid. Carbohydrate must, therefore, have been newly synthesized in the starved organism. According to Thierfelder the proteins furnish the material for this synthesis.

This formation of glycogen in animals subjected to inanition has been demonstrated experimentally by Zuntz and Vogelius, Rolly and others. Zuntz and Vogelius made rabbits glycogen-free with strychnine, which in toxic doses produces convulsions leading to a rapid consumption of the glycogen and to its practical disappearance from the tissues. Animals killed immediately after the convulsions ceased contained no glycogen or only slight traces in their tissues. The animals which were killed and analized several days later, though they received no food in the meantime, were found to have considerable quantities of glycogen (0.3 to 0.4 gm. in the livers, and 1.289 to 1.568 gm. in the rest of their bodies).

Pflüger also showed that at no time of inanition does the organism become glycogen-free. In a dog which fasted 28 days and suffered a considerable loss in weight, he still found large quantities of glycogen (4.8% in liver, 0.16 in muscles, 0.027 in skin, 0.009 in blood) all of which must have been produced synthetically from other constituents of the organism—fat or protein—since the supply generally present in the body lasts only for a few days of inanition.

The synthesis of carbohydrate in the fasting organism is of great importance in the interpretation of the metabolic processes.

2. *Fasting Metabolism of Lower Animals.*

Our knowledge of the inanition metabolism of lower organisms is still imperfect owing to the great difficulty of obtaining reliable data, especially on the respiratory exchange of these animals. Lesser studied the chemical processes in earthworms during protracted inanition. He found that up to the time when the worms lost a third of their body weight they subsisted chiefly on protein and glycogen. The average respiratory quotient (i.e., the ratio between the eliminated carbon dioxide and the oxygen taken in) was 0.877, which, of course, corroborates that the metabolism of the worms was predominantly of carbohydrate

and protein. The energy requirements for the first nine days of starvation were met in the following manner. The worms excreted 0.19 gram nitrogen representing a total energy yield of 5.3 Calories; the oxidation of 0.2503 gram glycogen and 0.31 gram fat furnished 1.06 and 0.3 Calories respectively. It is clear, therefore, that of the total of 6.66 Calories about 80 per cent came from protein, about 18 from glycogen and only a little over two from fat. Since the worms weighed 43.5 grams, the daily energy production per kilogram of starving worm was 15.3 Calories.

In a later stage of the fast (21 to 28 days) much greater quantities of fat are metabolized, but the glycogen still plays an important part in the metabolism. In the case of another starving worm which resembles the earthworm, the intestinal parasite *Ascaris*, Weinland could find no evidence of fat metabolism for the first ten days of inanition. Certain other differences in the fasting metabolism of these two genera of worms are observed which are due to the fact that in *Lumbricus* the decompositions are always complete while in *Ascaris* the glycogen is split into carbon dioxide and fatty acids.

Interesting observations were made by Brunow who experimented with crabs (*Astacus fluviatilis*). The energy exchange of the normal and starving crabs can be easily surveyed in the subjoined table:

Source	Metabolism of Energy at 14° C. (in Calories)			Metabolism of Energy at 20° C. (in Calories)		
	Beginning of Fast	80 Days Fasting	140 Days Fasting	Beginning of Fast	80 Days Fasting	140 Days Fasting
Protein	0.9016	0.6216	0.3670	1.2320	0.8513	0.6826
Carbohydrate	0.1298	0.0596	0.0176	0.5645	0.2407	0.0970
Fat	0.0124	0.0095	0.0143	0.0551	0.0437	0.0732
Total Calories	1.0438	0.6907	0.3989	1.8516	1.1357	0.8528
Per cent of energy from non-protein source	13.6	10	8	33.4	25	20

The total metabolism of the crab diminishes with the fast, and this diminution is especially pronounced at the lower temperature. Furthermore, at the lower temperature the diminution in the intensity of the metabolism is gradual, whereas at the

higher temperature the fall is more abrupt in the early period of the fast. This, of course, is due to the fact that the available supplies of the organism are more quickly used up because of the more active metabolism under the higher temperature.

It will also be noted that by far the greater part of the total energy of the starving crab comes from protein (86.4 to 92% at 14° C., and 66.6 to 80% at 20° C.). The energy from both the protein and carbohydrate diminishes throughout the fast, while that from fat metabolism increases during the advanced stages of inanition so that this source yields more energy towards the end of the fast than at the beginning.

3. *Metabolism of the Fasting Guinea Pig.*

Passing to the higher organisms our knowledge of the chemical processes in inanition is more comprehensive. We shall consider the fasting metabolism of representatives of three different animal groups—the guinea pig, the dog and man—first, because they represent different degrees of metabolic activity; secondly, because they also represent distinct nutritional types.

METABOLISM OF FASTING GUINEA PIG

Days of Fast	*Body Weight Gms.*	*Nitrogen Excretion Gms.*	*Total Calories*	*Calories from*		*Energy from Protein %*	*Calories per Day and per Kgm. (Average)*
				Protein	*Non-protein Source*		
1.	672	0.200	101.1	5.30	95.8	5.3	157.3
2.	625	0.417	102.6	11.05	91.55	10.8	
3.	582	0.395	89.9	10.5	79.4	11.2	
4.	550	0.332	77.1	8.8	68.3	11.4	
5.	524	0.332	72.4	8.8	63.6	12.1	148.2
6.	498	0.343	75.5	9.1	66.4	12.0	
7.	474	0.205	74.4	5.4	69.0	7.3	
8.	450	0.285	65.1	7.5	57.6	11.5	153.1
9.	428	0.294	69.1	7.8	61.3	11.3	

From the above table containing the results obtained with a guinea pig which fasted nine days (Rubner) we may learn several important things. In the first place it will be noted that about 11.5 per cent of the energy used up during the fast comes from protein. The amount of protein katabolized in the first day of fasting is very small. This is due to the fact that the glycogen which contributes a large part of the energy requirement in the beginning of the fast spares the protein from de-

struction, a phenomenon which, as will be shown in this chapter, is practically universal. From the third to the sixth day the nitrogen elimination in the urine remains nearly constant. The total metabolism, having diminished sharply since the second fast day, now also stays constant within narrow limits. Since guinea pigs generally lose about eight per cent of their weight in the first day of fasting, we can estimate that the animal lost about 15 per cent of its initial weight in the first two days. The average metabolism during this time was 157.3 Calories per kilogram and per 24 hours. The next five days, during which the body weight diminishes 20 per cent more (from 15 to 35%) represent a period of relative metabolic stability. The daily expenditure of energy is only 148.2 Calories (average), which is the lowest level for this animal. The last two days of the fast obviously group themselves into another definite period. The loss in body weight by the end of nine days approaches 45 per cent; the nitrogen elimination also shows a decided change from the previous, or middle period. During this advanced period of starvation the organism begins to suffer pathological changes. The total metabolism per kilogram rises to 153.1 Calories, but an examination of the fourth column in the table shows that the heat production of the starving guinea pig undergoes a new abrupt change, so that a new metabolic phase ensues on the eighth day. A similar condition will be met with again when we consider the metabolism of the fasting dog and man.

4. *Metabolism of the Fasting Dog.*

One of the most thorough and far-reaching contributions to fasting metabolism is Avrorov's investigation on starving dogs. The animals were kept in a calorimeter without food or water, and consequently they were under ideally uniform conditions of temperature, moisture, ventilation and bodily repose. The experiments were carried on uninterruptedly until death occurred, which in the four dogs used varied from 17 to 66 days. The daily heat production was determined directly with the calorimeter; the carbon dioxide production, the oxygen consumption as well as the water vapor exhaled every 24 hours were regularly determined. The urines and feces were analyzed for nitrogen and carbon; besides, at the close of each experiment the cadavers of the dogs were also completely analyzed.

The fasts were preceded by a preliminary period of a few

days' duration. During this time the animals received an adequate diet and the study of their protein and gaseous metabolism showed that they were in a condition of physiological equilibrium at the time the inanition experiments commenced.

Already during the first day of fasting the oxygen consumption and carbon dioxide production—and, of course, the total heat produced—very suddenly decrease by 10 to 20 per cent as compared with the same in the preliminary period. Although the gaseous metabolism may continue to decline somewhat further in the next few days usually about the fourth day of the inanition, the metabolism reaches a new level and for a considerable length of time remains fairly constant at this lower level. The animals thus quickly readjust themselves to the requirements of the changed situation, and, as was already shown for the guinea pig, the basal metabolism (i.e., minimum energy production) stays unchanged until in the more advanced stages of inanition a still further drop occurs. An abrupt decrease takes place in the last few days of the fast just preceding death from exhaustion.

5. *Four Stages in Inanition.*

Dividing the entire course of the inanition into four periods—each period comprising approximately one-fourth of the total loss in weight sustained at the time of death—and averaging the results which were obtained by Avrorov with all his dogs, we can gain a clear conception of the essential changes taking place in the chemical dynamics of the starving animal which are otherwise obscured by the mass of details. This division into four separate periods is not arbitrary but follows the actual sequence of events in inanition. It is all too often overlooked by those who study the problem of inanition that the closing of their experiment in no sense, physiological or otherwise, represents the natural termination of the fast. Furthermore, the length of time which the animal has fasted offers no criterion of the effect produced by the deprivation of nourishment. It should be recalled here that Lasarev demonstrated how the changes in the different organs are definitely related to the particular stage of inanition. In comparing the chemical processes observed in one fasting animal with those in another it is important that it should be done for comparable phases of the fast. Some animals survive inanition longer than others, depending upon their state of nutrition, race and even individuality.

In every complete inanition we can distinguish four more or less sharply marked off phases: First, the period of transition from the condition of adequate feeding to the basal metabolism of fasting. The period that follows is characterised by the fact that the physiological activities are at a minimum peculiar for this individual; it is divisible into early and late phases which, however, are not very distinct but merge gradually one into the other. These intermediate two periods are followed by a fourth, frequently well marked off, period. This final stage of the fast is characterized by the predominance of pathological phenomena caused by the prolonged stringency of nourishment and exhaustion of the tissues. In a general way these periods are marked by a corresponding fraction of the total loss in body weight at the time death occurs.

6. *Gaseous Metabolism of the Fasting Dog.*

With this theoretical consideration in mind we may now survey Avrorov's results with the starving dogs:

Average per Kilogram and per 24 Hours

Period	*Carbon Dioxide Liters*	*Change in P. C.*	*Water Vapour Gms.*	*Change in P. C.*	*Oxygen Consumed Liters*	*Change in P. C.*	$\frac{CO_2}{O_2}$	*Calories*	*Change in P. C.*
Normal.....	10.77		12.50		13.44		0.802	63.50	
Fasting I	8.68	—19.6	9.65	—22.8	11.03	—17.9	0.787	55.40	—12.8
" II	9.04	—16.1	9.20	—26.4	12.34	—8.2	0.732	55.96	—11.9
" III	9.77	—9.3	10.08	—19.4	13.70	+2.0	0.713	61.53	—3.1
" IV	10.44	—3.1	10.91	—12.7	14.39	+7.2	0.725	67.90	+7.0

During the first period of inanition the production of carbon dioxide and of water vapor also the consumption of oxygen undergo a very striking diminution. Calculated on a "per kilogram" basis these show an increase again in the last two periods, the oxygen consumption increasing most rapidly and exceeding the normal consumption already in the third period. This, of course, is associated with a change in the relative amount of fat which is being metabolized. The elimination of water vapor changes very slowly while the carbon dioxide production per kilogram increases somewhat more rapidly. It should be borne in mind, of course, that the "per kilogram" basis is but a rough index since with the loss of preformed water and glycogen and

the progressive exhaustion of tissue proteins and of fat, the kilogram of body weight is substantially no longer the same during the different periods of inanition. We can understand, therefore, why the caloric output per kilogram, which after an initial drop at the beginning of the fast, remains very nearly constant for a long time, rises even above the normal value (by seven per cent) in the last period, when the much emaciated organism is relatively richer in protoplasm and poorer in reserve materials.

Contrasting the "per kilogram" metabolism with the "total" metabolism of an individual dog the difference becomes most prominent. I select for this purpose the dog which fasted 66 days having lost 62 per cent of its body weight. This dog maintained its functional equilibrium before fasting on 505 Calories a day. During the first inanition period it produced only 424 Calories per day (16.8%). During the intermediate periods which lasted considerably over a month the daily heat production, though continuously declining, was on the average about 306 Calories per day. In the last period, and especially in the week just preceding death, the heat production diminished rather abruptly to 204 to 144 Calories per day.

It is not easy to account for this tendency of the gaseous exchange and for the caloric output per kilogram of body weight to increase in the course of inanition. The first explanation which suggests itself is that with the withdrawal of nutrient material from the tissues the cellular elements in a unit of body weight gain preponderance; in other words, in the same mass of substance there are now more cells. Since the cells are not only the ultimate units of structure but also of physiological activity, it is clear that the same mass of tissue is the seat of a more intensive metabolic exchange.

7. *Nitrogen Metabolism of the Fasting Dog.*

It is not enough to know the gaseous exchange to interpret the manifold transformations of matter in the organism during inanition. We must know also the waste products eliminated through the kidneys. Later on we shall take up in detail the urinary excretion during inanition. At present we will limit the discussion to a review of Avrorov's data obtained with four fasting dogs, arranging these as before according to the phase of inanition.

Period	Quantity of Urine c.c.	Grams Eliminated per Kilogram and per 24 Hours						
		Nitrogen	Differ. %	Carbon	Differ. %	Carbon from Fat	Differ. %	Percentage of Total Carbon from Fat
Normal.	200	1.31		6.79		2.49		36.7
Fasting								
I	56	0.30	—77.1	4.91	—27.7	3.93	+57.8	68.0
II	49	0.38	—71.0	5.06	—25.5	3.82	+53.4	75.5
III	47	0.48	—66.4	5.63	—17.1	4.20	+68.7	74.6
IV	40	0.38	—71.0	5.94	—12.5	4.70	+88.8	79.1

The gradual diminution of the average daily quantity of urine is of no particular significance since the dogs fasted without water. The changes in nitrogen and carbon elimination in the urine deserve more close examination.

8. *Premortal Rise in Nitrogen Elimination.*

The nitrogen excretion per kilogram rises gradually until the end of starvation. Shortly before death—especially in some animals—an abrupt increase in the nitrogen elimination occurs which is symptomatic of the approaching termination of the fast. This increase is designated as the "premortal rise," and has been observed by many investigators in different animals (Voit, Falck, Heymans, Schimanski, Rubner, etc.). It is held by some (Voit) that the premortal increase in nitrogenous waste products results directly from an increased protein katabolism coincident with the exhaustion of the supplies of fat. It must be pointed out, however, that animals which died from starvation show frequently even microscopically appreciable amounts of fat. The cadavers of starved dogs usually contain two per cent of fat. Avrorov's dogs after death still possessed an amount of fat equal to over 15 per cent of the total residual protential energy. Schulz and his school argued from precisely such facts that the premortal rise in nitrogen elimination is associated with a sudden onset of an extensive cellular disintegration, but the evidence they adduced in support of this view is not conclusive. Zuntz contends that the premortal increase in protein katabolism must be conditioned by some form of auto-intoxication, and theoretically this is a plausible explanation. The fact that the substances

generally described as extractives tend to accumulate in the tissues of starved animals strongly supports such an hypothesis.

Mansfeld and Hamburger suggest the possibility that the premortal rise in nitrogen excretion is connected with thyroid activity. It is well known, for instance, that defective oxidation, in whatever way it may be produced, leads to an excessive nitrogen elimination; this does not occur, however, in thyroidectomized animals. Mansfeld and Hamburger found that whereas the nitrogen excretion may increase 110 to 180 per cent in the last two days of inanition, this increase does not exceed 15 to 20 per cent in rabbits that were thyroidectomized. But thyroidectomy also prolongs very considerably the survival time in inanition (Marinesco and Parhon), so that a greater quantity of nitrogen is eliminated prior to the time when a premortal rise ordinarily occurs, and this may perhaps explain the failure of an increased premortal nitrogen elimination.

Heilner and Poensgen found that although rabbit serum in the early part of the fast possesses no proteolytic action, such enzymatic activity develops in the more advanced stages, and this they hold to be responsible for the premortal rise so often noted in nitrogen elimination.

This increased proteolytic power of the serum in advanced stages of fasting receives a somewhat different interpretation through the researches of Jobling and Petersen. According to these investigators the increased enzymatic activity is brought about by an unbalancing of the ferment-antiferment equilibrium due to a disappearance of the antitrypsin during inanition. They offer, furthermore, evidence to show that the loss of ability to inhibit tryptic digestion is paralleled by a rise in the non-coagulable nitrogen of the serum which in turn goes hand in hand with an increased nitrogen elimination through the kidney. In other words, according to Jobling and Petersen, the premortal rise in nitrogen excretion is due to the partial disappearance of serum antitrypsin. This leads to an accumulation of protein split products which poison the system and thus occasion the death of the animal. Such evidence, therefore, directly supports Zuntz' hypothesis of an autointoxication in the advanced phase of starvation, and indirectly the view held by Schulz and his followers.

The conditions responsible for this unbalancing of the ferment-

antiferment equilibrium of the serum are not definitely established by Jobling and Petersen but their experiments suggest that the decrease in antiferment content may result from a diminution in the blood lipoid. If, however, the premortal rise in nitrogen elimination is indirectly brought on by a loss of lipoids, Voit's view gains new significance though in a much revised form. It would seem that the premortal rise is not associated with a complete disappearance of fat from the organism but with a depletion of the blood lipoids which unloosens the ferment action of the serum on the body proteins.

Reicher's studies of the blood picture with the aid of the ultramicroscope obtain great significance in this connection. Reicher finds that fine fat globules appear in the dark field after three or four days of fasting, i.e., just at the time when the reserves of glycogen have been practically exhausted. The association between carbohydrate metabolism and the appearance of these fine fat globules is experimentally demonstrated by administering *per os* cane sugar to a starved animal. Under this condition the blood picture under the ultramicroscope changes very quickly, the fat globules again disappearing from the field. Reicher further observed that the marked increase in nitrogen elimination in advanced stages of inanition is invariably connected with the disappearance of the fat globules from the blood. Where the fat does not disappear entirely the nitrogen excretion runs an even course until the death of the animal. As still further proof that the premortal rise is associated with a radical change in the fat katabolism, Reicher mentions the fact that preceding the premortal rise in nitrogen excretion there is an abrupt falling off in the elimination of acetone bodies.

E. Voit showed that the quantity of protein katabolized during starvation depends upon the amount of fat contained in the body. The rise in protein metabolism, especially the "premortal rise" is governed by this law of the ratio between the nitrogen content and the fat content of the organism. With the progress of the fast this $\frac{\text{N-content}}{\text{Fat-content}}$ ratio increases, and correspondingly the nitrogen excretion through the urine becomes greater. The percentage of the total energy output derived from the proteins rises proportionately. This law of the reciprocal relationship between fat and protein as sources of energy during inanition applies not only to the progress of the fast in the same individual,

but may likewise be observed when different individuals are compared:

Animal	*Initial Fat Content*	*Loss in Body Nitrogen at Time of Death*
Dog	19%	22%
Dog	11	35
Fowl	26	26
Fowl	9.1	39
Fowl	2.7	41

9. *Carbon Metabolism of the Fasting Dog.*

Returning to the consideration of the results of Avrorov, we observe an increasing elimination of carbon in the urine with the progress of the fast. The important thing to note in this connection is that this carbon is chiefly of a non-protein origin; the carbon derived from fat, which in the prefasting period was 2.49 gm., increases to 4.7 gm. in the last period of the fast, i.e., almost 89 per cent. Avrorov did not clearly appreciate that this increased carbon in the urine was due to the appearance of acetone bodies. That such an interpretation of his urinary findings is correct is borne out by a comparison of the total carbon excretion with the carbon derived from fat. Already in the first period of the fast the former decreases about 28, while the latter increases 57.8 per cent, and continues to increase throughout the whole fast.

The consumption of fat greatly increases in inanition while the katabolism of the protein is much reduced. This accounts for the fact that whereas in well fed dogs 85 per cent of the total carbon elimination is in the form of carbon dioxide, the starved dogs (on an average for the entire fast) eliminated 94.5 per cent of carbon as carbon dioxide, one of the chief oxidation products of fats. The total energy production is apportioned between the proteins and the fats according to Avrorov as shown in the table on page 139.

About 15 per cent of the total energy (on the average) used up during inanition was obtained from the combustion of protein; the remaining 85 per cent coming from non-protein sources; in other words, about one in every seven days of fasting the dogs were sustained on protein. In the case of the guinea pig the proteins yielded about 11.5 per cent of the total energy requirement.

Heat Production per Kilogram and per 24 Hours

Period	Total Calories	From Protein		From Fat	
		Calories	Per Cent of Total	Calories	Per Cent of Total
Normal	64.7	34.0	53.2	30.7	46.8
Fasting					
I	55.8	7.4	13.1	48.4	86.9
II	56.5	9.4	16.5	47.1	83.5
III	62.6	10.9	17.2	51.7	82.8
IV	67.3	9.5	14.0	57.8	86.0

10. *Minimum Protein Metabolism.*

The share of the total energy expended in a prolonged fast which is furnished by the proteins is indicative of the minimum amount of protein (differing for various animals) absolutely essential to the continuance of existence. This protein minimum varies, of course, with the individual, depending on sex, age, temperament, state of previous nutrition. The level of protein metabolism during feeding depends entirely on the quantity consumed with the food, but in fasting the minimum of protein metabolism is, so to speak, automatically established. Since for the greater part of fasting the organism is in every respect physiologically normal, the minimum thus established (at any rate in the first half of the inanition) may be regarded as the true physiological minimum.

Though as carriers of potential energy proteins are inferior to fats, from a biological point of view they are of incomparably greater importance. Fats and carbohydrates are very necessary in the economy of the organism but not absolutely essential, while proteins are indispensable for continuance of life itself. Most of the metabolic processes occurring in the cells, synthetic as well as destructive, are reactions of the protoplasm of which the proteins are the physical basis. Even the utilization of the fat stored in the body is only made possible through cellular activity, since the oxidation of fat at body temperature is impossible without the intermediation of the complex cellular mechanism. Proteins which are the essential components of protoplasm of both cells and nuclei have a great dynamic function to perform in inanition while the other organic substances serve merely as stored supplies to be drawn upon as need arises.

11. *Participation of Carbohydrates in Fasting Metabolism.*

In discussions on metabolism of starving animals too much emphasis is usually laid on the purely destructive phenomena. The continuous formation of glycogen in the fasting organism has already been alluded to; this involves synthetic processes producing molecular rearrangements of considerable amplitude. Avrorov, for instance, quite erroneously considers fats and proteins as the only source of energy in the fasting dogs. But recalculating his data for one dog with the aid of the non-protein respiratory quotient [1] I find unmistakable evidence that carbohydrate is oxidized besides fat, which occurs on nine out of the seventeen days during which the dog fasted.

Of course, we have no means of telling how much fat is converted into carbohydrate and how much is directly oxidized. The respiratory quotients obtained by Avrorov in his metabolism experiments fall frequently below 0.70, which is the theoretically expected quotient if fat alone is burned. He made altogether 188 determinations of the respiratory quotient of which 39, or over one-fifth are below 0.70 (the lowest varying from 0.65 to 0.67), which indicates only one possible thing, namely, that the carbon dioxide eliminated is *less* than would be produced from the katabolism of fat with the quantity of oxygen consumed. In other words, some of the oxygen does not form carbon dioxide but is retained in the body in molecular combination as when a substance poor in molecular oxygen (fat or amino acids) is transformed into a substance relatively rich in intramolecular oxygen (glycogen). This may be illustrated by the theoretical formula:

$$100 \text{ g. Fat} + 84 \text{ g. } O_2 + 7.4 \text{ g. } H_2O = 191.3 \text{ g. Glucose}$$

[1] By "non-protein respiratory quotient" is meant the ratio between the volumes of carbon dioxide produced and oxygen used up in the oxidation of fat and carbohydrate only. The protein katabolism is known from the nitrogen excretion in the urine, and a gram of urinary nitrogen corresponds to a consumption of 5.91 liters of oxygen and a production of 4.75 liters of carbon dioxide from katabolized protein. The gaseous exchange corresponding to the fat-carbohydrate metabolism is easily calculated, being the difference between the total gaseous exchange and that derived from the protein. More oxygen is required for the complete combustion of fat than of carbohydrates, and the $\frac{CO_2}{O_2}$ ratio varies from 0.70 to 1.00 according to the relative amounts of fat and carbohydrate in the mixture. From the table prepared by Zuntz and Schumberg we can find the proportion of each corresponding to the non-protein quotients ranging between the limits of 0.70 to 1.00.

In the formation of carbohydrates from fat it must be remembered, of course, that there are two possibilities of derivation either from the glycerine or from the fatty acid radical.[1] Though such transformation has never been absolutely proved, it must be remembered that it has never been disproved either, and it has certainly never been shown to be chemically improbable. On the contrary, Ringer and Lusk [2] demonstrated beyond any doubt the formation of sugar from such amino acids as glycocoll and alanin, also from glutamic and aspartic acids. The need for carbohydrates is so relentless that the organism, unable to obtain these with its food, tries to satisfy this need under all circumstances, using every available method for this purpose.

The carbohydrate synthesized in the fasting organism would in all probability be quickly consumed tending to raise the respiratory quotient, while the synthesizing process itself would have an opposite effect. The gross respiratory quotient must, therefore, be regarded as the resultant of many factors, often antagonistic to each other. The purely mathematical consideration of the respiratory quotient fails to grasp its true biological significance.

Bardier's experiments on the respiratory exchange of starving geese may be mentioned in this connection. These animals generally contain immense quantities of fat. It has been demonstrated beyond a doubt that this fat is formed from the carbohydrates in their food. The transformation of carbohydrate into fat has a distinct effect on the gaseous metabolism of these birds which finds its expression in respiratory quotients exceeding one (1.0) in value (for detailed discussion see Morgulis and Pratt). Bardier experimented with two exceptionally fat geese which he subjected to fasting for seventeen days. The carbon dioxide production which in the prefasting period was 609 and 544 c.c. per kilogram and hour respectively, diminished rapidly to 418 and 451 c.c. on the first day of fasting, then remained fairly constant for about 12 days. The fact of particular importance for us is the radical change in the respiratory quotient during the fast. In the geese before fasting this varied from 0.75 to 0.89, but it declined to 0.52 to 0.53 in the first five days of starvation. These extremely low quotients indicate that fat is probably converted into glycogen when the geese fail to obtain carbohydrates

[1] Cremer, M., *Ergebnisse d. Physiologie,* I, 888, 1902. Wohlgemüth, J., *Ibid.,* 167, 1910.

[2] Ringer and Lusk, *Ztschr. physiol. Chem.,* 66, 106, 1910; also *J. Am. Chem. Soc.,* 32, 671, 1910.

which are a predominent constituent of their normal diet; in other words, when there is a stringency of food as in inanition a reversal of the chemical processes occurring in the abundantly fed geese may possibly take place.

12. *Metabolism of the Fasting Man.*

Men have frequently served as subjects for metabolism investigations on the effect of fasting. A thorough knowledge of the character of the katabolized material and of the sources of energy during a prolonged fast, while the person lives upon his own body substance, is of more than passing interest. All the scientifically studied fasts of men have been of relatively short duration. In the longest fast of this kind lasting 40 days Succi lost only 25 per cent of his original weight. Judging by the loss of weight, therefore, the experiments on inanition with human subjects have not extended far beyond what may be regarded as the second stage of inanition and, regardless of the length of time of the abstinence, had no deleterious effect whatever upon the subjects because the fasts were invariably discontinued long before the exhaustion stage had been reached. Unquestionably the most completely studied human fast is that of Levanzin, recorded in the publications of the Carnegie Institution (Publ. 203, edited by Benedict).

During his 31 day fast Levanzin spent every night (12 to 13 hours) in a specially constructed bed calorimeter, and his gaseous metabolism as well as the heat production were measured directly. His metabolism for the remaining hours of the day was determined in a series of short respiration experiments, and the heat production calculated indirectly.

In the table below the more important findings pertaining to the metabolism of Levanzin are briefly summed up. For purposes of simplicity the results are presented as daily averages in four separate groups, each group comprising one-fourth of the fast. As will be shown later, Levanzin's fast extended over two inanition periods, the first two groups, therefore, representing the first and the last two groups the second inanition period. The grouping of the results by half periods is undertaken for purposes of convenience as it permits a bird's-eye view of all the essential facts much better than the tabulation of the daily data in full would do.

Period	Liters CO_2 Produced	Liters O_2 Consumed	R. Q.		Katabolized Grams of			Calories from			Calories Produced	
			Non-Protein	Total	Glycogen	Fat	Protein	Glycogen	Fat	Protein	Total	Per Kilogram
I a.	260.4	352.6	0.720	0.740	24.1	134.7	59.2	102.0	1284.6	262.0	1648.4	28.70
I b.	219.5	303.2	0.706	0.724	4.05	115.4	60.5	17.1	1125.4	267.4	1409.9	26.18
II c.	193.7	272.3	0.691	0.712	...	110.1	49.3	...	1049.0	217.3	1266.3	24.81
II d.	192.9	270.3	0.695	0.714	...	110.4	46.4	...	1052.8	205.0	1257.8	26.02

By the end of 31 days Levanzin lost about 20 per cent of his weight. Assuming the maximum loss he could possibly have survived as 40 per cent, it is clear that the fast could have extended another month before a fatal termination. In other words, the fast was broken at a relatively early stage, which fact must be borne in mind in interpreting the results. Comparing his condition with that of Avrorov's dogs, it is clear that Levanzin is still within the limits of the second inanition period. A review of the data will completely sustain this contention, and, furthermore, will prove that inanition in different animals follows the same general course. The results given in the first two divisions represent the metabolic events while Levanzin lost about 10 per cent in weight; they cover, therefore, what we have designated as the first inanition period. In this period, which in the guinea pig lasted only two days, in Avrorov's dogs (on an average) about 12 days, and in the case of Levanzin 15 days, the organism is readjusting itself from the prefasting metabolic level to the level of the true physiological minimum characteristic for the particular individual. It will be observed that the carbon dioxide production and oxygen consumption decrease very appreciably in this period. Unfortunately the data for the normal or preliminary period are not as complete as those which were obtained with Levanzin during fasting; therefore, it is not possible to calculate to what extent his metabolism in the first two weeks of fasting has actually diminished. It is, nevertheless, obvious that the total metabolism has undergone a considerable diminution, since in the second half of the first period the carbon dioxide and oxygen values still decrease 15.7 and 14 per cent respectively. This 15 day period represents, therefore, the transition from the metabolism of the well nourished condition to that of the fasting condition.

The change in the total metabolism can be estimated more readily by the daily heat production. Before the fast began Levanzin's heat production per day (on the average) was according to Benedict 1846 Calories. Since this calculation is based on the direct calorimetric measurements carried out while the subject was asleep, it will be proper to add at least 10 per cent to this to cover the extra energy loss during the waking hours when the subject engaged in various activities. In other words, Levanzin's total metabolism before fasting was 2,030 Calories per day which is the usual for a man of his weight (60.5 kg.) and moderate activity. In the first fifteen days of fasting this diminished by nearly 31 per cent (19 per cent in the first seven days). In the next period (16 days) we observe that the daily production of carbon dioxide and consumption of oxygen remains practically constant. The new level of metabolic equilibrium has thus been attained, and although the body weight diminished about 10 per cent as in the previous period the decrease in total metabolism (in terms of Calories produced per day) was only 10 instead of 31 per cent, which was the change in the earlier period.

Glancing through the table again it will be seen that in the early part of the first period 24.1 gram of glycogen was katabolized yielding 6.2 per cent of the total energy metabolism. The heat production from protein was 15.8 per cent of the total, the remaining 78 per cent being furnished by fat. It is, however, more important to study this distribution day by day. On the first day of fasting 68.8 grams of glycogen were used up, 38.5 grams on the third day and on the fourth and fifth the quantities were even less, 4.3 and 15.1 grams. The protein katabolism in the meantime varied inversely to that of the glycogen, increasing from a minimum of 42.6 grams, on the first day of fasting, to 71.2 grams on the fourth day, when also the smallest amount of glycogen was consumed.

In the later part of the first period the data of the metabolism experiments indicate that glycogen contributes only 1.2 per cent of the total energy requirement (4.05 gm. per day). The amount of fat consumed also diminishes very markedly (about 14.5%), while the protein katabolism is somewhat greater because less glycogen is now available.

The next period, as already noted before, is characterized by the relative constancy of the total metabolism and of the gaseous

exchange. It will be noted further, that the fat katabolism per day also remains constant, while that of the protein, after an abrupt fall (18.5%) since the previous period declines gradually within the next sixteen days. So far as the metabolism data can be appraised, carbohydrate consumption contributes nothing appreciable to the general energy fund during this period.

We cannot, however, agree with Benedict's view that *no* glycogen partakes in the metabolism of the second period. In the first place, the non-protein respiratory quotients for this period frequently fall below 0.70, the quotient for pure fat combustion. As a matter of fact, of the 16 respiratory quotients obtained during this period only six reach 0.70, and the rest vary from 0.68 to 0.69. Although this difference may not seem very important at first sight, it must be pointed out that practically one-half of the metabolic exchange has been computed from data obtained in a few short respiration experiments. The respiratory quotients which were found for Levanzin in the calorimeter experiments when the gaseous metabolism was studied continuously for 12 hours and longer, are almost invariably about two points lower than the quotients calculated from the brief experiments performed during the day. The presumption is therefore strong that the recorded respiratory quotients are too high rather than too low, and the fact that they fall below 0.70 must be interpreted as indicating a continuous formation of glycogen, possibly from fat.[1] It is, of course, probable that the quantities synthesized from day to day are readily consumed, leaving little surplus glycogen to be stored in the tissues, and although its oxidation may yield an insignificant fraction of the total energy produced, yet the biological importance of the carbohydrate moiety in metabolism is so little understood that it seems hazardous to neglect it entirely because quantitatively it is small. If the continuous participation of carbohydrate in the fasting metabolism has not been actually proven, neither has there been

[1] Low respiratory quotients have been found with other men who voluntarily submitted themselves to prolonged fasting. Thus—

DAYS OF FASTING

Subject	1	2	3	4	5	6	7	8	9	10
Cetti	0.72	0.68	0.68	0.65	0.66	0.67	0.67	0.68	0.67	0.68
Breithaupt	0.87	0.74	0.73	0.73	0.63	0.66	0.69	0.72		

incontestable proof to show that the metabolism is one exclusively of fat and protein. In Benedict's study of Levanzin, the most outstanding feature of which is excellence of the technique, we note that no carbohydrate was katabolized on the sixth and seventh day. Since carbohydrates are the most easily oxidizable substances and are invariably the first to be utilized in metabolism, this gap between the fifth and the eighth day can only be explained on the assumption that either the technique was not as faultless as one is apt to think or that after the glycogen had been exhausted a new supply was added through synthesis. It seems altogether improbable, however, that a 48 hour interruption in carbohydrate metabolism could have occurred.

13. *The Rôle of Carbohydrate in the Metabolism of the Fasting Man.*

From the point of view of the participation of carbohydrates in the general metabolism of inanition (Levanzin) three stages can be distinguished. The first day of fasting when a liberal store of glycogen is available, when there is no β-oxybutyric acid in the urine and the urinary acidity as compared to that of the preceding days of feeding is greatly diminished. From the second day on the urinary acidity rises very sharply, then gradually reaches a maximum (130% over acidity of first fast day) at the same time as the carbon dioxide tension in the alveolar air diminishes by 4 mm., indicating a tendency towards an increased blood acidity. All these radical changes in the chemical processes of the organism coincide closely with the progressive exhaustion of the stored glycogen. The urinary acidity having reached a maximum again declines to about the level obtaining on the first fast day. This second stage comprises therefore the time—neither sharply delimited nor showing any regularity as to duration in different individuals—during which small but still measurable amounts of glycogen partake in the metabolism. In the case of Levanzin a sudden increase in the urinary acidity paralleled by a new drop in alveolar carbon dioxide tension (indicating a change in the acidity of blood) occurs at about the sixteenth day of fasting. Until the closing of the experiment—fifteen days later—the alveolar carbon dioxide tension remains unchanged at this lower level, while the urinary acidity again gradually diminishes to the level of the first fast day and within narrow limits of daily variation also stays constant. This stage

coincides with the period of fasting when the carbohydrate participation in the general metabolism is not apparent; it is the stage when the synthesis of carbohydrate barely keeps pace with its oxidation, so that at best only small quantities may be retained by the tissues. So far the hypothesis is in complete accord with the facts generally observed in inanition. The derangement of the protein and fat metabolism resulting probably from alterations in the colloidal state of the protoplasm is especially strong in babies, for instance, who have a higher plane of metabolism. We will take up this point again presently. I wish to suggest here merely that the death from starvation—with the general train of events just preceding and accompanying it, such as premortal rise in nitrogen excretion, the rise in urinary creatine, the general lowering of the metabolism, the fall in body temperature, etc.—that all these are simply incidental to the organism's loss of ability to form carbodydrate *de novo*. This is also sustained by Michaïlesco's discovery that as the loss in body weight approaches the 40 per cent limit the glycogen disappears entirely from the tissues. The serious degenerative changes ultimately leading to the death of the organism are due to this phenomenon.

b. Urine and the Partition of Nitrogen.

Through the respiratory exchange we gain knowledge of the total metabolism, but in order to gain an insight into the chemical processes which occur in inanition attention must be directed also to the other channels of excretion, the kidneys, and the product of their function carefully examined. The nitrogenous wastes leave the organism principally by this avenue; hence, the changes in the composition of the urine acquire much interest.

For this purpose the analyses of Howe and his collaborators on the urines of starving dogs are particularly well adapted, especially the experiment extending over 117 days which is the longest fast on record. In this exceptionally long fast the animal's weight changed from 26.2 to 9.8 kilograms, i.e., it sustained a loss of 63 per cent. Following the plan adopted in presenting the data on the general metabolism, the author computed the average daily excretion of the different urinary constituents according to the particular inanition period, each comprising one fourth of the total loss in body weight (1–17, 18–42, 43–74, and 75–117 day).

TABLE VI

Period		Nitrogen Distribution						
		Total	Urea	Ammonia	Creatinine	Creatine	Purine	Allantoin
Normal	Grams	15.588	13.434	0.635	0.410	0.343	0.065	0.035
	% of total	.....	86.2%	4.07%	2.66%	2.20%	0.42%	0.23%
Fasting Periods								
I	Grams	4.487	3.576	0.307	0.285	0.060	0.025	0.031
	% of total	.....	79.7%	6.85%	6.33%	1.34%	0.56%	0.69%
II	Grams	3.288	2.675	0.213	0.208	0.005	0.012	0.004
	% of total	.....	81.3%	6.48%	6.32%	0.15%	0.37%	0.12%
III	Grams	3.018	2.515	0.254	0.183	0.008 [1]	0.016	0.012
	% of total	.....	83.25%	8.42%	6.07%	0.26%	0.53%	0.40%
IV	Grams	2.594	2.205	0.202	0.075	0.029	0.008	0.009
	% of total	.....	85.0%	7.78%	2.89%	1.12%	0.30%	0.35%

[1] During this period an excessive amount of water was consumed.

The total nitrogen elimination diminishes very abruptly with the beginning of the fast (from a daily average of 15.588 to 4.487 gm.) which is not at all surprising in view of the fact that the dog subsists on a diet very rich in protein. The significant fact, however, is that the daily nitrogen elimination for the two intermediate periods, II and III, remains very nearly the same. Thus, between the normal and the first inanition period the change in the daily average elimination is 71.2 per cent; between the second and first periods, 26.8 per cent; but between the two intermediate periods extending over 67 days the total nitrogen elimination diminishes only 8.2 per cent. In the fourth period which we have already learned to regard as the stage of approaching exhaustion and ultimate failure under the strain of inanition, a more or less abrupt diminution (13.8%) is seen to occur again.

The nitrogen excretion for the first several days of fasting is of so much importance that it should be followed day for day. The nitrogen voided in the urine during the first day was still quite large (9.326 gm.) but already in the next two days it declined to a very low level (2.029 and 4.532 gm.). On the fourth day, however, it again exceeded 9 grams. The series of changes in protein katabolism here sketched, which portray a universal occurrence in inanition, will be interpreted subsequently in con-

nection with the discussion of the nitrogen partition in the urine of fasting man.

Turning now our attention to the various nitrogenous waste products and their relative quantities in the urine at different stages in inanition it will be observed that the bulk appears as the most completely oxidized nitrogenous waste product—urea. In the urine of the fed dog this constituted 86.2 per cent of the total nitrogen excretion. In the first inanition period this diminished to 79.7 per cent of the nitrogen, but in the subsequent periods it gradually increased again reaching nearly the original proportion (85%) during the most advanced phase of inanition. The fact that the percentage of urea decreases in the early part of fasting gave rise to the erroneous hypothesis of a progressive decrease in urea excretion, which of course holds true only for fasts of short duration. Where the experiment extends beyond the first stage the gradual rise of the percentage of urea is invariably observed.

The excretion of ammonia is associated directly with the developing acidosis and ketonuria, which we shall discuss more fully subsequently. The organism's most immediate and direct means of guarding against acids set free in metabolism is through neutralization with ammonia and the elimination of the ammonium salt with the urine. As the laid by store of glycogen is used up and synthesis supplies only very small amounts to partake in the general metabolism, the usual phenomena resulting from a lack of carbohydrate in the diet follows; and along with the developing acidosis we find that the ammonia nitrogen, which before the fast formed 4.07 per cent of the total nitrogen excretion, rises to 6.85 per cent (average) in the first inanition period. It was already mentioned that on the fourth day the nitrogen excretion exceeded by almost five grams that of the previous day, which sudden increase was ascribed to the fact that the reserve glycogen had been completely exhausted, and at the same time the dog excreted the largest quantity of ammonia nitrogen (0.63 gm.) showing that the acidosis was severest then.

The percentage of the total nitrogen in the form of creatinine is much greater than in the fed dog, but with the progress of the fast it gradually decreases from an average of 6.33 per cent (Period I) to 6.07 per cent (Period III). It is significant that in the fourth inanition period—the period of ensuing ex-

haustion—the creatinine nitrogen elimination suddenly drops to only 2.89 per cent of the total nitrogen.

The urine of the fasting dog at a certain time becomes practically creatine-free, but the behavior of the creatine excretion likewise depends upon the particular period of the fast.[1] Thus in the first period of readjustment the absolute quantity of creatine diminished six times, but it still constituted 1.34 per cent of the total nitrogen eliminated (2.2% in the fed dog). In the next two periods characterized by functional equilibrium at a minimal metabolic rate the creatine of the urine diminished almost to the vanishing point, forming only 0.2 to 0.3 per cent of the total nitrogen. In the last period, however, the creatine reappears in much increased quantity, being again on the average 1.12 per cent of the nitrogen excreted in the urine. The rise in creatine excretion which begins only after two and a half months of starvation coincides with the rapid decline which takes place at the same time in the creatinine excretion. The premortal rise in nitrogen excretion is accompanied by what Howe and his collaborators describe as the "creatine-creatinine crossing," i.e., the crossing over of the two curves, when the results are plotted, the creatine nitrogen rising while the creatinine nitrogen is falling off.

The elimination of purine base nitrogen and of allantoin shows a tendency to decrease with the progress of the fast.

Studying the changes in the non-protein constituents of the blood of fasting dogs Morgulis and Edwards[2] find that the creatinine remains remarkably constant while the creatine either gradually increases or, following a diminution during a considerable part of the fasting time, it increases suddenly in the very advanced stage of the fast. This invariably present high creatine level in the late inanition stage coincides with the urinary findings of Howe and Hawk, who noted the rise in creatine excretion dur-

[1] This statement needs qualification. The fact has been demonstrated by a number of investigators and for a variety of animals that creatinuria is usually brought on by inanition. It is well, however, to remember that the condition which causes creatinuria is probably not starvation *per se*, but is perhaps some starvation effect. At any rate, the creatinuria of starvation is a usual but not an invariable occurrence. It is practically impossible, under certain circumstances, to induce creatinuria in fasting pigs. The creatinuria must therefore be associated with some metabolic effect of inanition, and probably results from a complexity of factors.

[2] Unpublished results.

ing the fourth inanition period. The uric acid content of the dog's blood is very small, but it increases continuously through the fasting period. This observation throws important light on the fact of a progressive diminution of allantoin elimination during starvation. It suggests, at any rate as a possibility, that the failure of the formation of allantoin from its uric acid precursor may be connected with defective oxidation.

1. *Partition of Nitrogen in the Urine of Fasting Man*

Turning now to a consideration of the nitrogen partition in the urine of fasting man, it should be remembered that in every known instance of human fasting we are dealing with the early phases of inanition. The urinary findings on Levanzin—being the longest fast extensively investigated—are unfortunately deprived of much value because there are no data available for the preliminary, or prefasting period, which is the natural starting point in the study of the changes in nitrogen partition during fasting. The investigation of Watanabe and Sassa on the urine of a man who fasted only 14 days—a research superior to Benedict's from a general scientific standpoint though much less voluminous—will be utilized also to supplement the deficiencies in the study of Levanzin's urine.

Levanzin's average daily nitrogen elimination prior to fasting was 13.98 grams, of which 0.64 gram, or 4.57 per cent was in the form of ammonia nitrogen. The full data are summed up in the table on page 152, arranged in four groups just as was done before with the data pertaining to the respiratory exchange and to the general metabolism, each two consecutive groups corresponding to the first and to the second inanition periods respectively.

It will be observed that the total nitrogen elimination which in the early days of the fast diminished very abruptly tends to rise during the second half of the first period, then (following another sharp fall) to remain more or less constant throughout the second period. In the well nourished condition Levanzin excreted 0.230 grams nitrogen per day and per kilogram of body weight; Kozawa, 0.237 grams; Cetti, 0.237; Beauté, 0.250; Succi, 0.274 (Florence fast) but only 0.141 in Naples and Rome.

TABLE VII

AVERAGE DAILY NITROGEN EXCRETION

Nitrogen Partition		Levanzin							Kozawa		
		Normal	*Period I*			*Period II*			*Normal*	*Period I*	*Period II*
			a	*b*	*a + b*	*a*	*b*	*a + b*		(*a* + *b*)	*a*
Total Nitrogen	Gr.	13.98	9.87	10.09	9.98	8.21	7.73	7.98	12.05	12.18	8.64
Urea N.	Gr.	....	7.50	7.42	7.46	5.68	5.53	5.60	....	....	....
	%	....	75.0%	73.5%	74.8%	69.2%	71.5%	70.4%	(86.7%)	(81.7%)	(75.7%)
Ammonia N.	Gr.	0.64	1.17	1.574	1.372	1.700	1.38	1.54	0.524	1.257	1.223
	%	4.57%	11.87%	15.6%	13.75%	20.7%	17.85%	19.3%	4.45%	10.3%	14.16%
Amino N.	Gr.	....	....	....	....	....	....	....	0.215	0.138	0.137
	%	....	...	....	....	....	....	....	1.84%	1.13%	1.58%
Uric Acid N.	Gr.	....	0.074	0.111	0.093	0.111	0.099	0.105	0.167	0.091	0.106
	%	....	0.74%	1.10%	0.93%	1.35%	1.27%	1.32%	1.42%	0.75%	1.23%
Purine Base N.	Gr.	....	....	....	....	....	....	....	0.020	0.018	0.019
	%	....	....	....	....	....	....	....	0.17%	0.15%	0.22%
Total Creatinine N.	Gr.	....	0.507	0.471	0.489	0.386	0.342	0.364	0.464	0.620	0.488
	%	....	4.63%	4.7%	4.9%	4.7%	4.43%	4.54%	3.85%	5.09%	5.65%

2. *Changes in Nitrogen Elimination in Relation to the Carbohydrate Reserve*

Levanzin's nitrogen excretion on the first fast day dropped to 0.118 grams per day and per kilogram but rose quickly and reached 0.207 grams on the fourth day, then with variations up and down it gradually declined to 0.146 grams nitrogen on the thirty-first day of fasting. In the case of Kozawa, who was on a *principally* vegetable diet before the fast, the nitrogen elimination for the first fast day declined only to 0.206 grams but on the fourth day reached the highest peak of 0.316 grams and then gradually diminished to 0.183 grams nitrogen on the fourteenth day of fasting. This transient decline in protein katabolism during the first few days of fasting is unquestionably due to the sparing action which the abundant carbohydrate supply exercises. Sometimes the sparing action appears most pronounced during the first fast day (Prausnitz) but this need not be necessarily the case, and the maximum nitrogen excretion may occur any time from the second to the fourth day of fasting.

Daily Nitrogen Excretion

Subject	*Normal*	*Fasting Day*			
		1st	*2nd*	*3rd*	*4th*
Beauté	16.45	10.51	14.38	13.72	13.72
Succi	17.85	15.19	12.13	15.25	14.08
Tosca	13.99	8.76	8.38	10.73	9.40
Succi	8.99	8.72	8.45	9.05	8.51
Levanzin	11.54	7.10	8.40	11.34	11.87
Kazawa	12.05	10.90	13.73	12.91	15.11

Although no hard and fast rule can be laid down which the changes in nitrogen elimination may be said to follow in the first few days of fasting, the important thing to note is the fact that the temporary diminution and the subsequent increase are correlated to the changes in the store of accumulated glycogen. This hypothesis finds support not only in the study of the participation of different organic materials in metabolism already alluded to, but is sustained also by direct experimental evidence. May showed that an injection of glucose into a fasting rabbit will cause a diminution in the nitrogen output in the urine, which happens also when through infectious fever the protein katabolism is greatly stimulated.

Wimmer showed that depending upon the quantity of carbohydrate fed as much as 55 per cent of the metabolised protein may be conserved.

Heilner demonstrated the possibility of limiting protein waste in inanition by means of subcutaneous injections of cane sugar. This author ascribes the sparing action to changes in osmotic conditions brought on by the cane sugar injection, but whatever may be the nature of the mechanism whereby the proteins are saved, the fact of their sparing remains indisputable.

The second inanition period is generally marked by a new drop in nitrogen elimination and, with the establishment of the metabolic equilibrium of the organism at a lower plane, the nitrogen excretion stays again fairly constant. The readjustment of the protein metabolism as well as of the metabolism in general coincides also with a readjustment of the alveolar carbon dioxide to a lower tension (Levanzin). It is not possible at present to construe the true relationship between these phenomena—the metabolic equilibrium at a lower plane and an acidity of body fluids greater than in the well nourished condition—but it seems highly probable that the coincidence is not merely accidental.

It was already pointed out that the transitory changes in protein metabolism were associated with a depletion of the carbohydrate stock in the early days of fasting. The fat metabolism shows likewise alterations symptomatic of a lack of carbohydrates, as for instance the appearance of acetone bodies in the urine. The acidity of the urine which we observed to undergo a series of interesting changes during inanition results from the coöperation of two factors: the excretion of acid phosphates and of acetone bodies. The latter indicates, therefore, that the acidity in fasting is in a sense a ketosis. Brugsch believed that the excretion of acetone bodies in fasting depended on the presence of an abundant mass of adipose tissue fat, but Folin and Denis have shown conclusively that obesity is neither a predisposing nor even a contributing factor to the onset or intensity of the acidosis occurring in starvation.

In Levanzin's case, for instance, 0.5 grams of β-oxybutyric acid appeared on the second fast day. On the third and fourth days when the store of glycogen was nearly all used up the β-oxybutyric acid excretion rose to 2.1 and 3.5 grams respectively, and was being eliminated continuously throughout the fast.

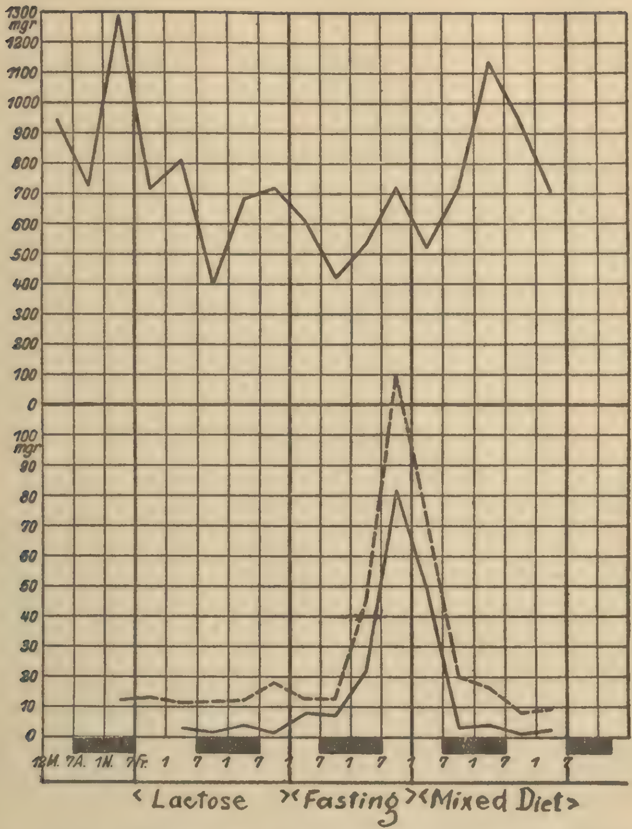

FIGURE 6.—The excretion of total nitrogen (upper curve), acetone and beta-oxybutyric acid (broken line curve) in the urine of babies on a full diet, on an exclusive lactose diet, and during complete fasting. (After Schlossmann and Murschhauser.)

In starving babies the appearance of acetone bodies in the urine is especially marked and prompt, as figure 6 shows. It will be noted that the administration of lactose very quickly relieves the ketonuria.

3. *Metabolism of the Fasting Baby*

The inanition metabolism of the baby is supposed to be distinguished by the fact that the nitrogen excretion per kilogram and per hour tends to increase from day to day. This is due partly to the fact that the small supply of glycogen is rapidly oxidized, and also to the fact that in the nourished baby protein serves primarily for building up of the tissues, the energy of maintenance being furnished by the fat and carbohydrates of the food. In fasting the baby is obliged to draw upon its own proteins for maintenance, especially as the small stock of glycogen is dwindling away, as is shown in the following experiments:

Fast Day Condition	*Nitrogen Excretion per Kilogr. and per Hour*		
	(*Schlossmann & Murschhauser*)	(*Keller*)	(*Benedict*)
Feeding	0.0036 g.	.....	.....
1st fast day	0.0051	0.0045	0.0065
2nd fast day......	0.0068	0.0038	0.0084
3rd fast day	0.0108	0.0044	0.0089
4th fast day	.....	0.0064	.....

Comparing these findings with those pertaining to the fasting adult already alluded to it will be seen at once that there is really no justification for the assumption that the rising nitrogen elimination is in any way peculiar to the fasting babies. The correlation between the nitrogen excretion and the participation of glycogen in the total metabolism may be appreciated from the following computation based on Benedict's data on fasting babies:

Fasting Day	*Grams*			*Calories*			*Per Cent of Total*		
	Protein	*Fat*	*Glycogen*	*Protein*	*Fat*	*Glycogen*	*Protein*	*Fat*	*Glycogen*
1st	0.94	2.10	1.69	4.15	20.00	7.15	13.3	63.9	22.8
2nd	1.21	2.61	0.62	5.35	24.90	2.62	16.3	75.7	8.0
3rd	1.28	2.54	0.36	5.66	24.24	1.52	18.0	77.2	4.8

4. *Changes in the Nitrogenous Waste Products*

The percentage of total nitrogen excretion in the form of urea in fasting man diminishes. This, however, is true of the condition prevailing in the early stages of inanition, and no carefully investigated human fast extended beyond that point. We have shown that as inanition advanced the urea tends to assume the same proportion as in the normal urine (dog). Even in experiments with human subjects this tendency may already be discerned. Kozawa excreted about 86.7 per cent of the nitrogen in the form of urea (this is not absolutely correct inasmuch as Watanabe and Sassa did not determine urea directly, and the 86.7 per cent includes also such minor constituents as allantoin, oxyproteic acids, etc., which, however, do not represent more than five per cent in aggregate. For comparative purposes it does not matter to assume the entire amount to represent nothing but urea). This gradually declined to a minimum of 74.4 per cent on the eighth day of fasting, then commenced to rise again, reaching 78.9 per cent on the fourteenth, or last day of the fast.

The urea excretion follows a similar course in the case of Levanzin. During the preliminary period preceding the fast the urea must have exceeded 80 per cent. Unfortunately this was not actually determined, but in the first week of fasting the urea nitrogen was on an average 75 per cent of the total excretion. It diminished to 73.5 per cent and, then, to 69.2 in the next two weeks, but in the last week of the fast it already rose again to 71.5.

The ammonia nitrogen excretion runs parallel and is reciprocal to the urea. We find, therefore, that the minimum percentage of urea nitrogen coincides with the highest point reached in the ammonia excretion, which in the case of Levanzin happens to fall on the seventh day, in the case of Kozawa on the eighth, etc. When with the progress of the fast there is a further increase in the urinary acidity—a moment which in Levanzin's fast has been shown to be associated with a diminution of the alveolar carbon dioxide tension, with the abrupt decrease in the total protein metabolism and the disappearance of *measurable* quantities of carbohydrate as energy yielders in metabolism—a new high point is reached in the ammonia excretion, which, however, again quickly and continually declines. It is safe to con-

clude, therefore, that the ammonia excretion follows closely the variations in intensity of the "hunger acidosis."

The amino nitrogen elimination has not been extensively studied. Brugsch using the phosphotungstic acid method found in Succi an increased amino acid excretion (from 2–3% to 3.7-6.9%). Watanabe and Sassa, employing the formal titration method, find little or no change in the amino nitrogen excretion (0.16 to 0.27 gm., or 1.4 to 2.1% in the foreperiod, and 0.11 to 0.19 gm., or 0.8 to 1.5% during fasting). It should be remembered, however, that Kozawa's fast lasted only 14 days and extended but slightly beyond the first inanition period. Fuchs experimenting with dogs and using likewise the formol titration method observed an increase in the absolute quantity of excreted amino acid nitrogen. In the first inanition period his dog excreted daily 0.0089 grams per kilogram, in the second period 0.0103, in the third period 0.0126 and in the last, or fourth period, 0.0213 grams. But while the actual quantity has thus increased two and one half times, in terms of per cent of the total nitrogen the excretion varied only between 2.45 and 1.96.

The amino acid nitrogen excretion is much greater in the rabbit than in the dog, but during inanition behaves in a similar manner. Thus, a rabbit eliminating normally 0.0228 grams amino nitrogen per day and per kilogram, excreted 0.0253, 0.0300 and 0.0452 grams in the successive periods of the fast. The per cent of the total nitrogen (in the form of amino nitrogen) varied from 2.25 to 2.33.

The excretion of purine bases and of uric acid in particular depends much on individual peculiarities. Cathcart found an abrupt diminution in uric acid excretion with the commencement of the fast (Beauté), but the excreted quantities increased in the course of the fast. Similar observations were made by Van Hoogenhuyze and Verploegh in their experiments with La Tosca, by Watanabe and Sassa on Kozawa and by Benedict on Levanzin.

Watanabe and Sassa found that the $\frac{\text{Purine Base N}}{\text{Total Purine N}}$ was 9.1 before fasting, but during fasting it diminished considerably, the daily ratios varying from 4.8 to 8.6, while with the resumption of feeding the ratio rose to unusually high values (12.9 to 22.8). This would seem to suggest that the conversion of purine bases to uric acid in fasting is imperfect.

It is important to note that the brief diminution in the uric acid (or total purine) elimination is followed by an increase which usually occurs when the body has lost 5 to 10 per cent of its weight. Lasarev in his study of the changes in weight of the various organs of guinea pigs at different stages of fasting (see p. 95) already observed that the spleen does not change in weight during the first period, but already in the second period it sustains practically the maximum loss. This sudden maximum reduction in bulk of the spleen is due to the loss of its mobile elements which, as will be shown in a subsequent chapter, probably migrate toward other organs. Nemser's investigation on the behavior of the nucleins in inanition is also suggestive in this connection. He found in fasting mice a relative increase in nucleic P_2O_5 ranging from 14.4 to 19.7 per cent in the liver, kidney and intestine, which may be associated with the transport of the mobile elements of the spleen to these organs. At any rate, the increased uric acid excretion must in some way be correlated with this migration of leucocytes from the spleen.

The total creatinine excretion in fasting is of double significance: first, in relation to muscle waste in inanition; secondly, in relation to the change in carbohydrate content of the organism. We will not reiterate what has already been stated in the preceding, nor is there any need to enter here upon a detailed discussion of this very perplexing question.

Following the case of Kozawa, we discover that during the prefasting period his total nitrogen excretion was 9.7 times as great as the total creatinine nitrogen, while during the 14 days of inanition the ratio was only 7.1. Assuming that the muscle contains 0.39 per cent of creatinine nitrogen, and 3.33 per cent of total nitrogen, the ratio is about 8.5. It would seem therefore hazardous to draw conclusions from such data as these with regard to the relationship between creatinine elimination and muscle waste, especially since other tissues rich in protein besides muscles sustain large losses in their nitrogenous content during fasting.

We may arrive at more definite conclusions with regard to the second point. Mendel and Rose showed that a lack of carbohydrate is the principal factor for the appearance of creatine in fasting urine, and this is also sustained by Palladino's more recent work. It must likewise be pointed out that any-

thing which will free the liver of its glycogen as, for instance, hydrazine[1] or will injure the liver's glycogenic function as chloroform or phosphorus[2] will at the same time cause the appearance of creatine in the urine. It seems probable that the rise in creatine excretion observed at the approach of death from starvation is connected with those degenerative changes in the liver which interfere with its proper glycogenic functioning, but may also be due to the complete disappearance of glycogen which according to Michaïlesco takes place in the most advanced phase of inanition.[3]

The daily variation in total creatinine elimination leaves little doubt as to its relationship to changes in the glycogen content of the body. Kozawa's total creatinine excretion during his 14 day fast is much greater than in the preliminary period. On the second day of fasting it suddenly rises from 0.473 to 0.624 grams, reaching a maximum of 0.692 on the fourth day. It then gradually declines and on the fourteenth day returns again to the prefasting level. This is essentially true also for Levan-

[1] Underhill and Kleiner, *J. Biol. Chem.*, 4, 165, 1908.

[2] Mendel and Rose, *ibid.*, 10, 1911.

[3] It is not to be overlooked that this statement will undoubtedly call forth vigorous objections from those who accept the view of the direct derivation of the urinary creatine from the preformed creatine contained in the muscles. It is not the author's intention to venture too lightly upon disputed ground. Even those most competent to offer first hand opinion on this much debated subject differ widely in their interpretation of the results. Benedict and Osterberg (*J. Biol. Chem.*, 18, p. 195, 1914) object to the view that urine creatine is derived from the muscle creatine. They experimented with phloridzinized dogs which eliminate large quantities of creatine in the urine. By supplying the dogs with enough protein in the food to secure nitrogen equilibrium these investigators were not able to check or reduce the creatinuria. From these experimental results they argued that the creatine of the urine could not therefore originate from the preformed creatine in muscle, but that the creatine must be a constant product of the intermediate metabolism. In the presence of carbohydrate the creatine presumably undergoes further changes in the organism, but in its absence it is eliminated in the urine. The possibility of muscular derivation of the creatine Benedict and Osterberg regard as precluded by the fact that the animals were in nitrogen equilibrium. These experiments are unquestionably very clean cut in their bearing upon the problem. Although their interpretation also harmonizes entirely with the view expressed above in the text, it must not be overlooked that nitrogen equilibrium does not necessarily prove that there is no katabolism of muscle tissue. It merely indicates that the intake and outgo of nitrogen is balanced. Possibly under the stringent conditions of carbohydrate demand by the tissues of the organism, either under the influence of phloridzin or in the advanced stages of inanition, the endogenous protein metabolism is affected in some manner not yet understood.

zin's total creatinine excretion. His total creatinine elimination reached a maximum of 0.53 grams on the fourth day of inanition, while measurable quantities of creatine did not appear until the third day. In both instances, it is evident, that this coincided in time with the nearly complete exhaustion of the glycogen reserves.

c. The Mineral Constituents of the Urine

The final products of fat and carbohydrate combustion are removed from the organism through the lungs with the expired air; the products of nitrogen metabolism, to a very large degree, through the kidney, but the mineral substances set free in the processes of katabolism find their way to the exterior either with the feces or with the urine. During inanition, when fecal discharge frequently ceases entirely, the urine may be regarded for all practical purposes as the sole avenue for the escape of mineral waste products.

The interest attached to the question of the inorganic metabolism in inanition is essentially with regard to the ultimate source of the material. Since the starving organism does not obtain any inorganic material from the outside, the mineral constituents in the urine must be derived from disintegrated tissue substance, except such minute amounts which may come from the drinking water. In some instances of human experiments (Succi) where mineral waters were taken during the fast, analysis of the inorganic constituents is, of course, without particular value.

Considering the inorganic constituents eliminated with the urine in fasting, it is necessary to distinguish between acid radicals like chlorine, phosphorus pentoxide, and sulfur trioxide, and the alkaline bases—sodium, potassium, calcium, magnesium. The former are present in the organism very largely in organic combination either as component parts of the protein molecule (S) or in various combinations with both proteins and lipins (P).

Although the data on inorganic metabolism in fasting are not very extensive, and few of the recorded results cover the entire course of inanition, it may nevertheless be stated that the problem of the source of the mineral constituents present in fasting urine is practically insoluble. The various hypotheses and interpretations construed from these results are but crude guesses at best. The premise that there is a single source—

for instance, the musculature—is fundamentally wrong, because the mineral constituents found in the urine during fasting have a multiple origin, and so long as we have no means to appraise the actual contribution which the individual tissues make to the fund from which the starving organism draws, it is futile to attempt to solve this problem of the ultimate origin of the inorganic substances. The urine represents the final chapter in the history of the fasting metabolism, but the events of the preceding chapters in that history are still largely a closed book to us. Nevertheless a consideration of the urinary mineral constituents throws side lights upon some interesting points regarding inanition which make such a discussion valuable.

1. *The Acid Radicals*

The source of chlorine in the urine for the first several days of fasting is somewhat uncertain. Judging by the fact that the ratio $\frac{N}{Cl}$ during the preliminary period is low, it is certain that most of this chlorine comes from the salt added as condiment to the food. The strength of this argument can be best appreciated by comparing the $\frac{N}{Cl}$ ratio for Beauté (Cathcart) with the ratio found in the case of Munk's dog. In the latter case, with no salt added to the food, the $\frac{N}{Cl}$ ratio before fasting was seven to eight times as large as for Beauté.

Human flesh contains approximately 0.07 per cent of chlorine, and we can, therefore, compute the total amount derived from that source using the nitrogen excretion as an indication of muscle metabolism. Leaving out of consideration the early part of fasting, when some of the chlorine is probably of exogenous origin, Beauté eliminated 0.340 grams of chlorine in the second half of his fast, but the theoretical amount which the muscle substance could yield would be only 0.184 grams. This large excess of chlorine (46%) must, therefore, have come from the katabolism of some other tissue richer in chlorine than the muscle substance.

The results obtained with Levanzin are even more note-

TABLE VIII

THE AVERAGE DAILY ELIMINATION OF INORGANIC CONSTITUENTS

Subject	*Levanzin*					*Beauté*			*Dog*		
Author	*(Benedict)*					*(Cathcart)*			*(Munk)*		
Period	*Normal*	*Fasting Period I*		*Fasting Period II*		*Normal*	*Fasting Period I*		*Normal*	*Fasting Period*	
		a.	*b.*	*c.*	*d.*		*a.*	*b.*		*I*	*II*
Nitrogen	...	9.87	10.09	8.21	7.73	16.26	12.01	8.76	16.82	5.34	4.01
Chlorine	...	1.076	0.290	0.160	0.140	6.47	1.64	0.34	0.266	0.091	0.045
$\frac{N}{Cl}$	...	9.18	34.8	51.3	55.2	2.5	7.3	25.8	68.4	58.7	89.1
P_2O_5	...	2.337	1.860	1.738	1.434	3.823	2.548	1.566	1.990	1.018	0.082
$\frac{N}{P_2O_5}$	...	4.2	5.4	4.7	5.4	4.3	4.7	5.6	8.5	5.3	4.9
Sulfur	...	0.620	0.610	0.530	0.510	1.377	0.760	0.571	....	....	....
$\frac{N}{S}$	...	15.9	16.5	15.5	15.2	11.8	15.8	15.4	....	....	....
Calcium	0.307	0.249	0.234	0.220	0.147	0.272	0.195	0.125	0.061	0.031	0.058
Magnesium	0.034	0.093	0.069	0.060	0.052	0.112	0.094	0.043	0.056	0.026	0.029
$\frac{Ca}{Mg}$	9.0	2.7	3.4	3.7	2.8	2.4	2.1	2.9	1.1	1.2	2.0
Potassium	...	1.437	0.898	0.654	0.658	3.160	1.147	0.594	....	....	....
$\frac{N}{K}$	...	6.9	12.4	12.6	11.8	5.2	10.5	14.8	....	....	....
Sodium	...	0.900	0.126	0.066	0.052	3.6[illegible]	0.388	0.148	....	....	....
$\frac{N}{Na}$	...	11.0	8.0	1[illegible]4.4	148.6	4.5	31.0	59.1	....	....	....
$\frac{Na}{Cl}$	...	0.84	0.44	0.41	0.37	0.[illegible]6	0.[illegible]4	0.44	....	....	....
$\frac{K}{P_2O_5}$	...	0.6[illegible]	0.48	0.38	0.46	0.83	0.45	0.38	....	....	....

worthy because his fast covers two inanition periods, and furnish thus information concerning a more advanced stage. Besides, the subject drank only distilled water. In the latter half of the first inanition period (I *b*) the chlorine elimination per day was 0.078 grams, or 27 per cent in excess of the theoretical amount had all the nitrogen come from muscle katabolism. But in the early and late parts of the second inanition period the excess was only 0.012 and 0.022 grams (7.5 and 15.7%) respectively per day. Of course, it is not justifiable to consider all the nitrogen as being derived from flesh. The excess chlorine probably comes from such other tissues as the mucosa, particularly rich in chlorine, and this assumption is warranted by the observation that these tissues are used up extensively in inanition.

This interpretation holds equally well for the dog. With a chlorine content of the muscle of about 0.033 per cent, its chlorine elimination for the first inanition period exceeds the maximum quantity which muscle could yield by 0.038 grams per day (about 42%), but in the second period the excess is only 0.005 grams (or +11%) per day. These results agree remarkably well with those observed for Levanzin.

The excretion of phosphorus pentoxide is an important factor in determining the urinary acidity. It was already pointed out that the acidity is partly due to the ketosis resulting from defective fat oxidation, and partly to the increase in acid cleavage products, especially the phosphates. The relationship between the titratable acidity (in terms of c.c. N/10 NaOH) and the P_2O_5 excretion can be easily demonstrated. In the case of Levanzin, for instance, the urinary acidity shows three high points reached on the fourth, on the ninth and on the sixteenth days of inanition respectively. The phosphorus excretion on these days likewise shows distinct increases.

The curve of P_2O_5 elimination follows very closely that of the total nitrogen excretion. The ratio $\frac{N}{P_2O_5}$, however, is much lower than the ratio expected if both substances were derived from the musculature. According to Munk the ratio $\frac{N}{P_2O_5}$ for all soft parts (muscles and glands) is 6.6; according to Lüthje, 7.2. An examination of the above table reveals that in fasting the ratio is very much less: for Levanzin, 4.22 to

5.43; for Beauté, 4.72 to 5.59; for Kozawa, 5.3 to 5.6; and for Munk's dog, 4.89 to 5.25.

The folly of attempting to derive the total excreted P_2O_5 from muscle katabolism is shown by the following consideration which betrays a complete lack of uniformity:

Subject	*Total P_2O_5 Excreted*	*P_2O_5 Expected (Muscle Katabolism)*	*Difference*
Levanzin	56.63	41.63	+15.0 g.
Kozawa	26.28	28.71	—2.41 g.
Beauté	28.80	21.88	+6.92 g.

Owing to this discrepancy between the $\frac{N}{P_2O_5}$ ratio in muscle and in urine, Munk concluded that the excess of phosphorus must be derived from the bony structures. Wellman even believes to have furnished experimental proof for this hypothesis. It should be noted, however, that the $\frac{N}{P_2O_5}$ ratio is low even at the very beginning of the fast when it is reasonably certain that the skeleton could not be involved. The weight of the bones in the early phases of inanition may actually increase (consult previous two chapters). The loss of mineral substance from the bones is unquestionably associated with the developing acidosis. Goto in a recent investigation on the effect of artificially produced acidosis in rabbits (by means of intoxication with mineral acids) found that the bones do not lose appreciable amounts of calcium phosphate. His observation that more extensive inroads take place into the calcium carbonate of the bones for the neutralization of the acidity [1] finds its counterpart in Gusmitta's analyses of the composition of the long limb bones of a fasting dog. In this case the per cent of $CaCO_3$ showed a distinct diminution, while that of the calcium phosphate was even greater than before the fast. If extreme acid intoxication fails to cause an appreciable removal of phosphates from bones, it is in the highest degree doubtful whether a slight acidosis of the early inanition can bring about such a condition. Of course, it must be admitted that at present with the facts still imperfectly known we cannot hope to offer an adequate solution for this problem. It is well to recall Nemser's

[1] Goto, K., *J. Biol. Chem.*, 36, 355–375, 1918.

discovery that in several of the glandular organs there is an increased content of nucleins (therefore also of P_2O_5, which is a component of the nucleo-proteins) during inanition. In this connection it is still more significant to review Slovtzov's results which will be found tabulated in the preceding chapter. Studying the distribution of phosphorus and nitrogen in normal and starved beetles Slovtzov pointed out the transformation of the organically bound phosphorus into inorganic phosphates. If we compare the nitrogen and phosphorus content of beetles before fasting (*a*) and after fasting (*b*), as well as in the material which was lost in the course of inanition (*c*), the following ratios are obtained:

	(*a*)	(*b*)	(*c*)
$\frac{N}{P_2O_5}$	7.7	8.7	4.8

This forms a most interesting series which proves that the ratio between the nitrogen and the phosphorus excreted (*c*) in no way serves to indicate either the normal or the altered relationship between nitrogen and phosphorus in the organism itself. Furthermore, the above series reproduces a condition very similar to that existing in the starving man or dog; namely, that the $\frac{N}{P_2O_5}$ ratio in the eliminated material is much lower than that characteristic for the composition of the organism, either before or during inanition. There being no skeletal structures in beetles, it is evident that Munk's hypothesis does not account for the facts.

The sulfur appears in the urine in three forms: as inorganic sulfates, ethereal sulfates, and as neutral or unoxidized sulfur. Cathcart determined each kind separately in Beauté's urine, and in the table which follows the average daily distribution (per cent of total sulfur) is recorded which the author calculated for the different phases of the fast.

Period	*Inorganic S.*	*Ethereal S.*	*Neutral S.*
Preliminary	80.6%	7.45%	11.95%
I fasting period a	78.3	5.60	16.10
I fasting period b	76.1	5.24	18.56

The amount of ethereal sulfates is distinctly reduced in the fasting period. This is chiefly due to the smaller quantity of indican produced in inanition as a result of lessened intestinal putrefaction, as was shown by Müller and, in more recent years, also by Sherwin and Hawk, and by Underhill and Simpson.

The neutral, or unoxidized sulfur moiety increases rapidly, however, as the fast progresses. Unfortunately we have no information regarding the neutral sulfur beyond the first inanition period, and it would be important to study the behavior of the sulfur partitioning through the more advanced stages of fasting. If the neutral sulfur may be regarded as an indicator of the organism's oxidative power, the results are in line with Pugliese's hypothesis that this is diminished in inanition.

The study of the urinary excretion of sulfur is especially interesting because it is a true integral part of protoplasm, occurring as a component of the protein molecule. The $\frac{N}{S}$ ratio for muscle substance is 13:3.

In the urine of Levanzin as well as in that of Beauté the $\frac{N}{S}$ ratio possesses a remarkable degree of constancy, the average ratios varying from 15.16 to 16.54 (L.) and from 15.35 to 15.81 (B.). In either case, however, it is to be noted that the ratio is higher than the theoretical were all the nitrogen derived from the muscles. There must, therefore, be some other source of urinary nitrogen which is poor in sulphur. It is possible that with the aid of the sulfur values it might be possible to compute the actual amount of flesh katabolized.

2. *The Alkali Bases*

To interpret intelligently the excretion of bases one must bear clearly in mind their unequal occurrence in the muscle substance and in glandular organs, also their unequal distribution in the tissues and in the fluids of the body. In muscle there is seven times as much potassium as there is sodium, but in liver there is only three times as much potassium, and in other organs the proportion of potassium to sodium is smaller yet. In starving rabbits Katzuyama found that after the first two days of inanition the elimination of the potassium begins to diminish at the same time as the sodium excretion increases, and this continues until the last phase of inanition is reached.

In the last period which precedes death the situation is reversed, the potassium excretion increasing while that of the sodium diminishes at the same rate. This can be best appreciated from an actual example. The percentage distribution of Na_2O and K_2O in the urine has been calculated and arranged according to respective periods of inanition using Katzuyama's results with starving rabbits:

Period of Fast	*Per Cent*		*Na_2O : K_2O*
	K_2O	*Na_2O*	
I	89.9	10.1	11.3 : 100
II	63.5	36.5	58.5 : 100
III	67.4	32.6	49.3 : 100
IV	81.6	18.4	21.4 : 100

The relative amounts of sodium and potassium excreted during the entire fast are not the same in every experiment, the proportion of potassium increasing with the increase in the loss in body weight:

Duration of Fast	*Loss in Weight (Per Cent)*	*K_2O*	*Na_2O*	*$\frac{K_2O}{Na_2O}$*
12 days	36	69.3	30.7	2.26
14 "	40.5	73.2	26.8	2.73
20 "	51.7	82.9	17.1	4.85

When we consider the sodium and the potassium elimination in man it is observed that the potassium in the daily urine diminishes less rapidly than the sodium. Examining the data found for Levanzin (see table p. 164) we notice that with the progress of the fast the elimination of potassium varies as 1:0.624:0.455:0.457, while the elimination of sodium varies as 1:0.096:0.058:0.048.

The distribution of K_2O and Na_2O in Levanzin's urine according to the particular inanition period was as follows:

Inanition Period	*Per Cent*		*Na_2O : K_2O*
	K_2O	*Na_2O*	
I	72.7	27.3	28.4 : 100
II	90.8	9.2	9.0 : 100

This is practically the reverse of the condition obtaining in the rabbit, which difference must be attributed to the fact that in the period preceding fasting the rabbit consumes food predominantly rich in potassium (vegetables). The sodium salt, on the other hand, predominates in human food. Hence on the first day of fasting Levanzin excreted not only relatively, but absolutely, more sodium than potassium, but on the second day the potassium already exceeded the sodium.

The $\frac{N}{K}$ ratio—disregarding the first few days of fasting (I *a*)—shows a certain degree of constancy which favors the assumption that the potassium is derived principally from muscle substance.

The $K:P_2O_5$ ratio is also sufficiently constant that it may perhaps be taken to substantiate the view that both are derived principally from the protoplasmic portion of the organism since both potassium and phosphorus are found chiefly as cell constituents. The high proportion of K to P_2O_5 during the control period in the experiment with Beauté is undoubtedly due to the influence of exogenous potassium. Aron in his investigation of the mineral excretion of fasting babies has also come to the conclusion that the potassium may be regarded as an indicator of the extent of protoplasmic destruction in inanition.

The $\frac{N}{Na}$ ratio, on the contrary, is subject to wide and irregular fluctuations which make it appear improbable that the sodium and the potassium could be derived from the same source. The $\frac{Na}{Cl}$ ratio, however, possesses a certain significance. Disregarding the findings for the first several days, this ratio varies from 0.372 to 0.435 (Levanzin). In Beauté's case it is 0.436. If we consider the second period only (L.) the ratio is 0.393, and this is practically identical with the quotient which would be expected theoretically if all the sodium and all the chlorine were derived from sodium chloride (= 0.397).

This would seem to favor the assumption that the sodium chloride in the urine is derived principally from the body fluids.

The excretion of calcium in the rabbit during inanition at first diminishes, but after the fourth day and until the animal's death it increases gradually from day to day. The magnesium

excretion diminishes from the onset to the termination of the fast.

In three experiments with starving rabbits Katzuyama found the following proportions of CaO and MgO in the urine for the entire duration of the fast:

Duration of Fast	*Loss in Weight (Per Cent)*	*Per Cent*	
		CaO	*MgO*
16 days	36.4	67.4	32.6
18 "	48.8	64.6	35.4
18 "	50.0	66.0	34.0

It is, therefore, evident that the elimination of CaO and of MgO in the starving rabbit maintains within narrow limits a definite relationship (approximately as 2:1) which is not affected either by the duration of the fast or the total loss in body weight sustained. This differs radically from the condition prevailing in the relationship K_2O: Na_2O, which changes from 2.3:1 to 5:1 with increasing loss in body weight suffered at the time of death from starvation.

In man we do not observe this temporary diminution in the calcium excretion preceding a gradual but steady rise. Whether or not in more advanced stages of fasting the quantity of calcium in the urine of man would be found to increase from day to day may only be conjectured from the fact that in the dog this is found to be the case. Munk's dog excreted more calcium (0.058 gm. daily instead of 0.031 gm.) in the later stage of fasting than he did in an earlier one.

The muscle substance contains *less calcium* than magnesium, while in glands there is *more* calcium than magnesium. The $\frac{Ca}{Mg}$ ratio for muscles of man (Magnus-Levy), and of the horse (Aron) is 0.33, while for the dog (Aron) it is 0.60. The $\frac{Ca}{Mg}$ ratio in the urines of various subjects is as follows:

Subject	*Inanition Period*	*Ca: Mg*
Man { Levanzin	I	3.04
	II	3.25
Man { Beauté	I	2.50
Dog	I	1.19
	II	2.00
Rabbit	I–IV	2.00

It is quite evident from this summary of the available data that it is not likely that the muscle substance is the only source from which the calcium and the magnesium are derived, nor is it probable that these elements are furnished to any appreciable extent by the bones, where the $\frac{Ca}{Mg}$ ratio is considerably higher. The importance of the glandular organs must not be overlooked as a source of the calcium and magnesium excreted with the urine.

CHAPTER III

PHYSIOLOGICAL PHENOMENA IN INANITION

The changes of a functional nature which the fasting organism undergoes are not sufficiently known. Information on this side of the problem one gleans from the literature only occasionally, extended systematic studies being very rare. In the early phases of inanition and even throughout the larger part of its course there may be little of any significance from a physiological standpoint. The one human fast of sufficiently long duration investigated from a variety of angles (Levanzin) failed to produce evidence of any notable physiological changes. Extensive psychophysical tests performed regularly with this subject for 31 days led to the general conclusion that "there was no lasting evil effect of the fast, either upon muscular strength or neural activity." In view of this absence of any marked alteration in the functional activity, it is especially interesting to note the great improvement which the fasting effected in Levanzin's visual acuity. At the end of his 31 days' abstinence from food Levanzin could see *twice* as far as he did at the beginning of the fast.

In considering the physiological changes occurring in inanition one must be guided by the same fundamental conception of a succession of distinct phases of inanition which was expounded in full in the preceding chapter and was shown to be essential for the proper interpretation of the complex phenomena of metabolism. Unfortunately we do not possess detailed and systematic investigations of the different organic functions, covering the entire period of inanition; therefore, in studying the facts recorded in the literature it is necessary to keep clearly in mind the range of inanition phases which the facts embrace.

It is commonly supposed that inanition is associated with anemia. The older students of the problem (Collard de Martigny, Chossat, Bidder und Schmidt) sustained their belief with experimental proof, but their methods of procedure in estimat-

ing changes in blood volume were so crude that their results did not find corroboration in later researches. The studies of Panum, Valentin, Heidenhain, Voit, etc., at least establish a valid presumption in favor of the view that the blood diminishes proportionally to the general decrease in body weight, so that the relative blood volume remains practically unchanged during inanition. The problem, however, could very profitably be reinvestigated with the aid of the newer and more accurate methods. Considering the important rôle played by the blood in the organism's functional activity, the subject deserves much attention.

a. Blood Pressure

One of the earliest investigations on the blood pressure during inanition was made by Kagan on dogs and his experiments include the advanced as well as the initial stages of inanition. Kagan's studies, however, are open to serious criticism (of which he himself was aware), first, on account of the operation which was performed in the experiments for the determination of the pressure; secondly, because the blood pressure in the fasting animals was frequently compared with the pressure in a different but normal animal. In spite of the fact that Kagan selected dogs which matched each other in size, age, temperament, etc., his conclusions drawn from a comparison of the blood pressures of different animals cannot be regarded as very valid. His statement, for instance, that in the early phases of inanition the blood pressure tends to rise (about 10% higher than the pressure of normal dogs) is not sufficiently substantiated and may be erroneous. On the other hand, many of his experiments show a diminution in blood pressure.

Carotid Blood Pressure in Dogs

Condition of Dog	*Loss in Weight*	*Average Pressure*
1. Normal	...	177 mm. Hg
1. Starved	11.0%	173
2. Normal	...	160
2. Starved	22.0%	154
3. Normal	...	147
3. Starved	26.0%	127
4. Starved	35.5%	166
5. Starved	42.0%	154
6. Starved	46.4%	41

In the sixth dog with a loss in body weight of nearly 47 per cent, in other words presenting a most advanced stage of inanition, the average carotid pressure was only 41 mm. Hg which is even lower than the pressure resulting from a loss of two-thirds of the entire blood volume through hemorrhage. The fall in pressure may, of course, be brought about by a variety of factors: diminished mass of blood, exhaustion of the vasomotor center, weakened condition of the heart or change in the peripheral vessels.

The first possibility may be ruled out because our present knowledge of the blood mass in inanition offers no support for this. Weakened and diminished activity of the heart, especially in very advanced stages of inanition, is undoubtedly associated with degenerative alterations in the myocardium. According to Manassein the cross striations of cardiac muscle fibers begin to disappear in the advanced stages. This degenerative change in the heart muscle cannot, however, be held responsible for the lowering of the blood pressure which is noted already in the very beginning of fasting.[1]

Kagan also observed that while normal dogs may survive a loss of blood through hemorrhage amounting to about two-thirds of the original mass, in a starving dog which lost 48 per cent of its weight the removal of less than one-third of the blood volume is fatal. This must be due to a still further lowering of the blood pressure below the danger point, since the pressure was already quite low.

The determination of the blood pressure in fasting men with the sphygmomanometer is free from the objections raised against Kagan's experiments. They all agree in revealing a prompt falling off of the pressure with the onset of inanition.

Subject	*Pressure Before Fast*	*Pressure at End of Fast*	*Days of Fast*
Penny	110 mm. Hg	90 mm. Hg	30
Beauté	108	88	14
Kozawa	110	103	14

In the prolonged fast of Levanzin, Benedict and his collaborators have determined daily the systolic and diastolic pressure with the subject sitting or lying down. The general trend

[1] Extensive dilatation of blood vessels was noted by Marchand and Vurpas in the brain and by Meyers in the spleen and pancreas.

of all the four curves which they plotted shows a distinct decrease in the arterial pressure during the first 15 days of fasting, i.e., during the first inanition period which in the previous chapter we learned to identify as a transition period. This constant falling off of the pressure is followed by either an average constant value or by a slight tendency of the pressure to rise in the last part of the fast (end of second inanition period). The pulse pressure, i.e., the difference between the systolic and diastolic blood pressures, shows likewise a falling off until about the fifteenth fast day, followed by a period of approximately constant values. This constancy of the systolic, diastolic and pulse pressures is reestablished during the second inanition period which, as was shown in the preceding chapter, is also the period of metabolic equilibrium at the minimum physiological level.

b. Respiration

The rate of respiration and the rate of the heart beat both change markedly during inanition. Bidder and Schmidt made the following observations on a starving cat extending over the last three and a half days of its existence. These represent, therefore, the condition prevailing in the most advanced stage of the last inanition period. The normal respiration rate of the cat was 26 to 28 per minute, and the normal pulse rate 170 per minute.

Hours Before Cat's Death	*Rate per Minute*		$\frac{\textit{Pulse Rate}}{\textit{Respiration Rate}}$
	Respiration	*Pulse*	
87	28	160	5.7
76	25	159	6.4
64	27	134	5.0
51	23	121	5.3
33	22	112	5.1
18	18	109	6.0
11	15	100	6.7
7	16	88	5.6

In rabbits, whose normal pulse rate is 130 to 140 per minute, during advanced stages of inanition the rate diminishes to about 65 to 70 per minute. Chossat observed that the respiration rate of starved pigeons changes from 31 to 23 per minute.

Levanzin before his fast began had an average rate of respiration of 10.5 per minute. His lung ventilation was normally 5.13 liters per minute, or 593 c.c. per inspiration. The changes which this underwent in the 31 days of fasting, comprising the first and the second inanition periods, is shown in the table below:

Period		*Respir. Rate per Minute*	*Lung Ventilation per Minute*	*Volume per Inspiration*
Normal		10.5	5.13 liters	593 c.c.
Inanition Period I	a	11.0	4.93	548
	b	11.8	4.59	474
Inanition Period II	c	12.9	4.78	449
	d	13.8	4.87	428

We wish to point out the following important facts. The rate of respiration increases gradually with the progress of the fast. The diminution of the lung ventilation is probably connected with the reduced alveolar carbon dioxide tension. It is worth noting that in the light of the interpretation applied to the metabolic phenomena of inanition, the marked decrease in total lung ventilation occurs in the first, or the transitional period of readjustment from the well nourished condition to the fasting condition. The second period during which the subject is already in a state of physiological equilibrium is marked by a fairly constant rate of ventilation. The rate of respiration and the inspiratory volume vary inversely to each other.

The lung capacity measured by the number of liters of air driven out in a maximum expiration, diminishes during inanition. Kozawa's vital capacity changed from four liters before fasting to three liters after a fast of only 14 days. Levanzin's normal lung capacity was not determined, but the progressive diminution occurring in the course of his fast is revealed in the following:

Fast Day	*Lung Capacity*
2nd	3.74 liters
7th	3.91
24th	3.15
25th	3.24
31st	2.71

This diminished lung capacity may explain Féré's observations that starving guinea pigs possess a smaller resistance to asphyxia-

tion than normal ones. In the latter asphyxiation takes place in about 3 minutes and 17 seconds, whereas after one day of inanition the animals were asphyxiated in 2 minutes and 45 seconds, and after four days of inanition, in 2 minutes and 33 seconds.

c. Pulse and Cardiac Activity

The pulse rate, which Bidder and Schmidt have shown for the cat to fall off very rapidly during the last period of inanition (period of exhaustion) merits special attention. The most complete observations on this point have been made by Benedict and his collaborators in their investigation of Levanzin.

Recalculating their numerous data I found the following average values for the different phases of his prolonged fast:

Period		*Pulse Rate per Minute*		
		Day	*Night*	*Average*
Normal		72.5	70.0 *	71.3
Inanition Period I	a	68.6	63.3	66.0
	b	60.9	56.8	58.8
Inanition Period II	c	57.8	53.0	55.4
	d	60.6	57.0	58.8

* If the pulse rate for the first night were included the average would be 76.5; since, however, the very rapid pulse that night was obviously due to the excited state of the subject who was to spend his first night inside a calorimeter, it was deemed best to leave this out of the calculation.

For the first three weeks of the fast the pulse rate diminishes continuously decreasing by more than one-fifth (22.3%). Benedict is laying too much stress on the relation between pulse rate and metabolism. While the rate of the heart beat may in a *general* way serve as an index of the physiological activity of the organism, it is assuming more than the facts warrant to regard the pulse rate as an invariable measure of the metabolic function. In the first place, the pulse rate is the resultant of a number of factors, each and all of which may be affected differently in inanition. It is certainly noteworthy that while the average pulse rate diminished 22.3 per cent the average metabolism (heat production per 24 hrs.) diminished 38.1. Furthermore, while the metabolism remains unchanged during the second period the pulse rate rises from 55.4 to 58.8 per minute. Levanzin's fast ceased soon after the pulse rate commenced to

increase and there is no means for determining what its further course might have been especially as there is no information either from human or animal experiments which would justify speculations on this score.

It is not easy to find an explanation for the fact that during the fourth week of the fast the pulse rate begins to increase, but it seems hardly probable that it is associated with a greater irritability of the heart. It should be pointed out, however, that this rise is coincident with the maximum respiration rate. When the ratios between the number of heart beats and the number of respirations per minute before and during fasting (Levanzin) are compared, the following interesting series of changes is obtained:

Condition	*Pulse Rate* / *Respiration Rate*
Normal	6.8
Inanition Period I a	6.0
Inanition Period I b	4.9
Inanition Period II c	4.3
Inanition Period II d	4.3

In other words, during the first or transition period the ratio undergoes radical alteration, but in the second period, when a new physiological level has already been attained, the ratio remains constant though much lower than in the days preceding the fast. The rise in the pulse rate is therefore proportional to the increase in the respiration rate which is probably occasioned by the excitation of the respiratory center owing to the developing acidosis.

Indeed, there is some evidence to show that the cardio-inhibitory center is affected by inanition, and this may serve to throw light upon this phenomenon of the tendency of the pulse rate to rise with the progress of the fast.

Aducco records some very interesting observations on this point. It is well known that in dogs and in many other animals the rate of the heart beat oscillates according to the respiratory phase, increasing during inspiration and diminishing during an expiration. Fredericq ascribed this change in rhythm to the heightened tonicity of the cardio-inhibitory center during expiration, though it is also possible that it should be caused by a lowered irritability of the center. Under the influence

of inanition this change of rhythm becomes extraordinarily accentuated, frequently appearing towards the close of the first 24 hours of fasting and becoming progressively more pronounced. In the case of some of his dogs Aducco found that while there were three beats in the two seconds of the inspiratory phase, only one systole would occur in the six seconds of expiration, giving thus an inspiratory heart rate of 90 per minute, and an expiratory rate of only 10 beats. With the further advance of the fast, however, this difference tends gradually to disappear, and the heart beats during the inspiratory phase become very numerous and tend even to invade the expiratory phase. This process continues until the retardation previously occurring in the expiratory phase disappears entirely, the heart beating at a uniform and rapid rate during both phases of the respiratory movements. This condition is found in the most advanced stage of the fourth inanition period and coincides, therefore, with the utmost exhaustion of the organism. It may be truly regarded as due to excessive irritability of the heart, possibly associated with autointoxication apparently occurring in the last stages of inanition. It should not, however, be overlooked that the increase in the heart rate may be due to the fall in blood pressure which according to Kagan's experiments on dogs becomes very great in the fourth inanition period. It is significant that once the animal has been brought to this condition it can no longer be saved by realimentation. The exhaustion involves primarily the nerve centers, and Aducco showed that stimulation of the vagus nerve soon after the dog's death causes inhibition or even total arrest of the heart. He considers, therefore, the failure of inhibitory impulses to reach the heart during the expiratory phase and the generally increased frequency of the heart beat as being of purely central origin.

This view may, however, be regarded critically, because the vagus itself also seemingly undergoes important alterations in the course of inanition. Busquet has shown that in frogs which fasted a few days stimulation of the vagus caused inhibition in 86 per cent of the animals and in only 14 per cent complete cardiac arrest was brought about. But in frogs which starved two months the situation was completely reversed, inhibition following vagus stimulation in 14 per cent of the cases and total cessation of the heart action in 86 per cent. Feeding the frogs for seven days restored the original response to vagus excitation.

Jordan observed that the vagus nerve of fasting dogs loses its irritability, which phenomenon becomes the more noticeable the longer the inanition. Moreover, Statkewitsch found extensive pathological changes in the cardiac ganglia of rabbits in advanced inanition.

Lawson, Morgulis and Guenther have studied the hearts of dogs subjected to prolonged inanition by means of the string galvanometer (unpublished results). In the case of one dog which fasted several weeks and had lost over 40 per cent of its weight the chief cardiac changes revealed in the electrocardiograms were the slowing of the heart and the distinct arrhythmia which developed early in the fast. The electrocardiograms have also revealed a certain degree of instability which were very much pronounced in the case of a second dog under our observation. This dog also fasted until its weight was diminished by about 40 per cent at which time it was again fed for two weeks. The electrocardiogram of this dog showed in the beginning, before the fast commenced, premature beats and a marked left preponderance. In the figure are reproduced five electrocardiograms selected from a total of 12 obtained with this dog. As far as it was within our control the electrocardiograms were always taken in the same manner with the animals invariably in the same fixed position. It will be noted, by following the R-wave in the third lead that the left preponderance disappeared completely during the period of inanition to reappear even somewhat exaggerated in the subsequent recuperation period. The T-wave which before fasting (A) was rather indefinite had become strikingly negative at the time the dog's weight had diminished 14 per cent (B) and later, when the loss in weight reached 40 per cent (C), it was again very decidedly positive. On the fifteenth day of refeeding the T-wave is once more negative (E).

The form of the P-wave remained fairly constant in all electrocardiographic records, except perhaps in the third lead in record E. Of course, the most striking changes occurred in the R-wave, as can be seen at a glance when the third leads are examined in the plate. Our electrocardiographic studies are still in a preliminary phase and until we have more data we shall refrain from drawing either inferences or conclusions from our observations. So far the results seem to argue against the assumption of a neurogenic origin of the observed alterations in

the cardiac cycle but only future experiments can be counted on to throw light upon the question raised in this discussion of the nature of the effect of inanition on the heart.

Few though these observations may be, they throw doubt upon the general assumption that the central nervous system suffers little or even no change as a result of inanition. This misconception is based upon the observation that the nervous system sustains a comparatively small loss in weight, which, however, is no indication of the actual severity of the change in the organ itself. The percentage of loss in weight depends largely upon the amount of reserve materials contained in the tissue, which are being quickly withdrawn to meet the organism's need for nourishment. The central nervous system having no appreciable stores of reserve material undergoes therefore a smaller proportional loss than other organs. It must be admitted, however, that so long as the stores of nourishment deposited in the organism last the central nervous system's requirements are well supplied and it can therefore maintain its functional efficiency longest, but in the period of exhaustion—the most advanced phase of inanition preceding the animal's death—the nervous system fails.

d. Thermoregulation

This break down of the efficiency of the central nervous system can also be seen in the oscillations of the body temperature in inanition. Heat is the chief energy manifestation of the chemical transformations which constitute the organism's metabolism. It is natural, therefore, that a lowering of the metabolism which takes place in inanition should be reflected in the thermogenesis, and hence also in the body temperature which is simply the resultant of the heat produced and heat dissipated.

In the early stages of fasting there is scarcely any noticeable change in the body temperature or only a slight tendency to decrease. Schimanski found that the average daily temperature (morning, midday and evening) of a starving hen shows a slight change from 41.5° C. to 41° C. during the first two periods of the fast (loss = 21%). In the next period (loss = 30%) the temperature drops to about 39° C. The hen died two days later. These last two days comprise the fourth inanition period (exhaustion) and the temperature fell first to 38.6° C. then, on the last day, to 32.8° C.

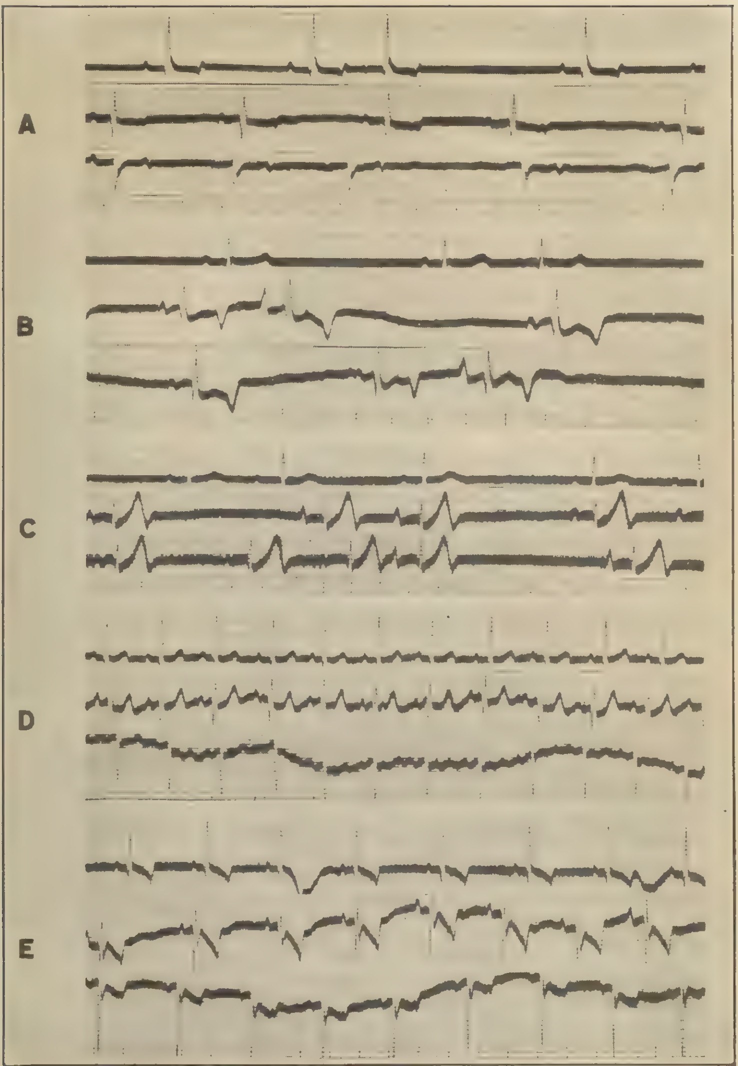

FIGURE 7.—The electrocardiograms A, B, C, D and E represent the records for dog 2 and were taken before the fast began (A), when the dog lost 14 per cent (B) and 40 per cent (C) of its weight as a result of fasting, and when the animal was fed once more on meat, (D) being the record on the first day after the feeding commenced and (E) on the fourteenth day. The three records in each electrocardiogram represent the three different leads. (Lawson, Morgulis and Guenther.)

Chossat experimenting with pigeons found that the maximum difference between the temperatures at midday and at midnight in well fed birds was 0.74° C., but the difference became more accentuated during inanition. Taking the average rectal temperature for the early period of inanition, middle period and final period we find the following significant changes:

Condition	*Midday*	*Difference*	*Midnight*	*Difference*	*Difference between Midday and Midnight Temperatures*
Normal pigeons	42.22°C.	...	41.48°C.	...	—0.74°C.
Starving pigeons:					
Early period (I)	42.10	—0.12	39.80	—1.68	—2.30
Middle periods (II & III)	41.90	—0.32	38.70	—2.78	—3.20
Final period (IV)	41.40	—0.82	37.30	—4.28	—4.10

The important facts here to note are: first, the progressive diminution of the body temperature; secondly, the much greater lowering of the midnight temperature; and, lastly, the gradually increasing amplitude of the daily temperature oscillations from 0.74° C. in the fed bird to 4.10° C. in the most advanced stage of inanition. The greater fall in the midnight temperature, of course, depends on the fact that the midnight air is generally colder, and the gradual increase of the difference between the temperatures taken twelve hours apart indicates that the thermoregulating mechanism becomes less efficient with the progress of the fast.

It is well to point out in this connection F. T. Roger's observations on pigeons: "Depriving the normal bird of food but not water for a period of five to seven days has little effect upon the body temperature. But during the second week of starvation the body temperature becomes subnormal, and after 14 to 15 days may be as low as 36° C. with the bird in a cage at the usual room temperature of 20° C. During this stage of starvation (*the last period of exhaustion*) the bird begins to lose its ability to maintain a constant body temperature and acts somewhat like a cold-blooded animal. Thus, at this time, exposure of the bird to cold is followed by a fall, and exposure to warmth is followed by a rise in body temperature. It is therefore possible by prolonged starvation of the pigeons to reduce it to a condition in which its body temperature is, in

part, a function of that of the environment. In all such experiments care has been taken that the starving bird shall always have plenty of water. Feeding the bird promptly brings the body temperature back to normal if, of course, starvation is not pushed until death is imminent."

At this stage it is not merely the thermoregulating mechanism that fails to function properly but the thermogenesis of the organism is seriously impaired, and—as Chossat has shown—the birds can still be saved if they are given nourishment and kept warm at the same time. Feeding alone is not sufficient to restore the birds to health once the mechanism of thermogenesis had been affected.

Lasarev found that the body temperature of guinea pigs remains unchanged until the weight has diminished about 10 to 12 per cent (i.e., for the first inanition period) and begins to decline when the loss reaches 18 to 23 per cent, i.e., at the close of the second or beginning of the third period. In the third period the temperature declines very quickly and may fall as low as 31° C. In the last, or fourth period, which finally terminates in death, the body temperature drops on the average to 25° C. (21.6 to 29.6° C.).

Opposite are introduced several records of the rectal temperature of a guinea pig and rabbit (Simonowitch), and of a dog (Avrorov) which were subjected to complete inanition (without food or water).

e. Physiology of Muscles

With the organism subsisting merely on reserves which it deposited in its tissues in times of plenty, how is the other manifestation of metabolic activity, namely, the capacity to produce mechanical work, affected? We may dismiss entirely such attempts at a solution of this problem as has been made by Maggiora, for instance, who finds with the ergograph of Mosso that the working capacity of persons who fasted but 24 hours is diminished. Apart from the general criticism which may be raised against the ergograph method the psychical influence upon the individual should not be overlooked. Indeed, Manca who repeated the ergograph experiments could find no evidence that a 24 to 36 hour fast made any difference in the amount of work performed, or in the speed with which fatigue appeared.

Animal	Loss in Weight	Temperature (°C.)		
		Morning	*Evening*	*Average*
Guinea Pig	*Normal*	39.0	39.0	39.0
	I 7.4%	38.0	38.8	38.4
	II 15.1%	38.0	38.2	38.2
	II 19.7%	38.1	38.6	
	III 25.0%	38.7	38.5	37.6
	III 28.1%	37.7	37.8	
	III 32.5%	37.4	37.4	
	IV 35.1%	35.0	36.4	35.2
	IV 36.6%	34.8	34.6	
Rabbit	*Normal*	39.4	38.6	39.0
	I 1.8%	38.6	38.9	38.8
	I 9.7%	39.0	38.8	
	II 10.6%	39.3	39.3	39.0
	II 15.2%	38.8	38.8	
	III 22.4%	38.7	39.0	38.7
	III 24.7%	38.6	38.4	
	IV 28.9%	37.4	37.2	36.8
	IV 34.8%	35.7	?	
Dog	*Normal*	38.2	...	38.2
	I 8.1%	38.3	...	38.3
	I 16.6%	38.3	...	
	II 24.2%	37.9	...	37.8
	II 31.0%	37.7	...	
	III 38.4%	37.8	...	37.7
	III 47.0%	37.6	...	
	IV 54.8%	37.2	...	36.4
	IV 62.0%	35.6	...	

Manca also worked with Mosso's ergograph, the subject lifting the weight both voluntarily and under direct electrical stimulation. Gaglio's study of the contraction of the gastrocnemius muscle (stimulation of sciatic nerve) of normal and starved frogs gives the first definite indication of a diminution in the contractile power of the muscle in inanition. Lee and Morgulis[1] investigated in a systematic manner and on a more or less extensive scale the question of fatigue and working capacity of muscles from starved animals. They used for this study the isolated diaphragm and the extensor cruris muscles of cats both well fed and starved for various lengths of time. The average results are tabulated on the following page.

[1] Unpublished results.

Loss in Body Weight	Number of Animals	Diaphragm				Extensor			
		Duration of Work in Mins.	%	Work Done Gm. Mm.	%	Duration of Work in Mins.	%	Work Done Gm. Mm.	%
Normal..	18	185	100	113,954	100	83	100	32,893	100
1 to 9%	6	142	77	139,131	122	93	112	36,715	112
10 to 19%	6	186	100.5	79,940	70	77	93	26,894	82
20 to 29%	13	111	60	62,953	55	42	51	21,471	65
30 to 40%	5	93	50	63,149	55	47	57	19,805	60

From these studies we concluded that both the extensor and the diaphragm muscle lose their working capacity and fatigue more quickly as the fast progresses, the decrease appearing first in the second inanition period (loss in body weight 10 to 19%). In the advanced inanition period (loss 30 to 40%) the work done and the duration of the work are both reduced to about one-half of that found for the normal cat. A circumstance of particular significance, however, is the marked increase in total work produced and its duration before complete fatigue sets in, which occurs in the first inanition period. Thus the diaphragm muscle of cats which lost about 10 per cent of their weight as a result of fasting performed 22 per cent more work measured in gm. mm., while the extensor muscle gained 12 per cent over the same muscle from well nourished cats. We are unable at present to advance an hypothesis to account for this temporary improvement in muscular strength under the influence of the brief fast. It is well to point out, however, that the records taken with Levanzin show a similar phenomenon. While the numerous strength tests instituted with this subject fail to betray any appreciable change for the worse in the course of his 31 day fast, the work which he performed with both his right and left arm shows a definite and considerable increase over that of the preliminary period. The maximum weight lifted with the left arm was 120 pounds, or about 7 per cent more than the normal, and this maximum had been reached on the sixth fast day. The maximum weight lifted with the right arm was 115 pounds (+ 17%) and this had been attained on the tenth fast day. It is not possible to ascribe this improvement in Levanzin's muscle strength to the effect of exercise, because the maximum efficiency was not enduring but soon commenced to diminish. We are bound to conclude, therefore, that the unmistakable improvement in his muscle strength was due to a different cause and, as

in the case of our starving cats, it also occurred within the first inanition period. Carlson, experimenting with a human subject, also reports that the daily 30-minute ergograph records showed an increase in strength and in endurance in the course of a 15-day fast.

f. Reaction to Drugs

In view of the fact that many diseases are complicated by a state of complete or partial inanition it becomes an eminently practical problem to know how the fasting organism responds to various drugs. Aducco, whose investigation was one of the earliest attempts at a solution of this problem, brought forward evidence of a very definite nature. He studied the reaction of starving dogs (with and without water) to such nervous system poisons as cocaine, strychnine and phenol, administered either by stomach tube or subcutaneously.

Cocaine hydrochloride was given in doses of 0.02 grams per kilogram of body weight. The effect of the drug was judged by the rise in temperature and by the intensity of the motor reflexes; both of these responses became more pronounced in the fasting condition. The responsiveness of the dogs increased with the progress of the fast. Thus, to cite just a single instance, the administration of 0.02 grams per kilogram of body weight on the eve of the fast caused the temperature to rise 1.45° C., and the motor reflexes were mild. When a similar dose was given to the same dog after it fasted 13 days, the rise in temperature was 3.8° C., and after 40 days of fasting 4.0° C. In either case the motor reflexes were very strong.

Similar results were obtained with strychnine. The sulfate was used and the dose was less than the lethal (less than 0.45 mg. per kg.). The dose which in the well nourished dog produced no effect or perhaps called forth only a mild reaction proved either fatal to, or at any rate caused a considerable rise in, temperature and violent convulsions in dogs already starving for some time. With phenol convulsions were likewise produced of such magnitude as could be caused only with much greater doses in dogs that were well fed. This may have been due to the diminished ability of the starving organism to oxidize the phenol (Pugliese).

Notwithstanding the fact that dogs vary greatly in their sensitiveness towards the drugs in question, Aducco's conclusion

is warranted that they produce a stronger effect in the state of inanition than in a nourished condition of the animal.

Delafuoy also found that starving frogs are more sensitive to strychnine than fed frogs.

Mansfeld investigated the effect of the group of narcotics: chloral hydrate, morphine, paraldehyde, ethyl alcohol, amyl hydrate, ethyl urethane. His numerous experiments on fed and starved rabbits are summed up in the table. This represents a compilation of all his results.

Exper.	*Narcotic*	*Effect of Drug on Fed Rabbit*	*Effect of Drug on Starved Rabbit*	*Days of Fasting*	*Loss in Weight (%)*
1.	Chloral hydrate	Very slight narcosis	Exitus letalis	8	28%
2.		" " "	" "	5	35
3.		" " "	" "	4	19
4.		" " "	Complete narcosis	9	18
5.	Paralde-hyde	Very slight narcosis	Exitus letalis	5	20
6.		None	" "	5	6(?)
7.		Slight restlessness	Complete narcosis	5	30
8.		Slight narcosis	" "	5	26
9.	Morphine HCl	Slight narcosis	Exitus letalis	4	30
10.		Drowsiness	" "	5	20
11.		"	" "	5	9.6
12.		No action	" "	4	29
13.		Slight narcosis	Strong convulsion	4	7
14.	Ethyl alcohol	Strong poisoning	Strong poisoning	4	18
15.		Deep narcosis	Deep narcosis	4	22
16.		" "	" "	4	26
17.	Amyl hydrate	Light narcosis	Light narcosis	7	27
18.		" "	" "	5	28
19.		" "	" "	5	22
20.		" "	" "	5	27
21.		None	" "	5	23
22.	Ethyl Urethane	Light narcosis	Light narcosis	4	19
23.		Deep narcosis	Deep narcosis	6	26
24.		" "	" "	5	20
25.		" "	" "	4	23
26.		" "	" "	3	24

From these results it is clear that the sensitivity of the fasting organism to the different narcotics is not affected to an equal degree; it is also noteworthy that those containing the ethyl radical do not differ in their action upon fed and starving animals. Mansfeld attempts to interpret his results on the basis

of the Meyer-Overtone hypothesis of the dependence of the narcotic activity of a substance on its differential solubility in water and in lipoids $(Q = \frac{\text{sol. lipoid}}{\text{sol. water}})$. The greater the solubility of a substance in lipoid than in water the more does the substance tend to accumulate in the lipoid-rich central nervous system. It will, therefore, exert a more toxic effect than other substances which, owing to their greater solubility in water, will become more uniformly distributed throughout the organism. On this hypothesis the greater effectiveness of the narcotics in the fasting animals is supposed to be the result of a *relatively* larger amount of lipoid in their nervous system as compared with normal animals. The extensive inroads into the fat deposits of the body during fasting leaves the nervous system as the chief lipoid-containing tissue, and, hence, more of the drug finds its way there. The hypothesis, however, is not applicable to the starving organism because we do not know what actual changes take place in the lipoid content of the nervous system, and whether or not the nervous tissue itself becomes enriched in water. The first premise of the hypothesis rests therefore on an assumption which still needs verification. Besides, some substances, like chloral hydrate for instance, owe their effectiveness to a special affinity for nervous tissue.

It is not surprising that the action of chloral hydrate, etc., in inanition is stronger because *relatively* to the rest of the organism the nervous system increases as the fast progresses, and the same dose will, therefore, produce more striking results owing to the greater concentration of the drug in the central nervous system. This is evident when we consider that a kilogram of body weight is not an immutable entity but is qualitatively very different in a well fed and in a starved animal. It changes continuously in the course of inanition, comprising not only different proportions of the fundamental chemical substances but of the various morphological components as well (see p. 99). The dosage of the drug on the basis of the unit of body weight loses therefore its *raison d'être* at least so far as starved organisms are concerned. The assumption is, of course, entirely gratuitous that the same relative quantity of the drug is absorbed by a fasting or well fed animal when the dose is calculated on the basis of the body weight. The lowered resistance of the organism in inanition may, therefore, turn out to be the response to

an overdose or at any rate to a stronger dose than was actually administered to the control.

On the other hand it should not be overlooked that the intracellular oxidative processes may be reduced in inanition and this may probably account for the greater toxicity of phenol, for instance; besides, we know practically nothing concerning the rate of absorption and elimination of drugs in fasting, which most likely are considerably modified in inanition. The last mentioned factors doubtless play an important part in the increased responsiveness towards the drugs. The matter seems therefore much more complex than Mansfeld apparently realizes when he attempts to explain everything on the simple mechanism of differential solubility in accordance with the Meyer-Overtone theory. So long as the factors above mentioned remain unelucidated, his interpretation of the reaction to drugs of the fasting organism will naturally fail to meet with approval.

The fact that the fasting organism is not more sensitive to substances which contain the ethyl radical (ethyl alcohol) need not be construed in the sense that, being very soluble in water, these substances do not accumulate primarily in the nervous system and thus fail to produce a greater toxic action. The fasting organism is able to burn alcohol in certain concentrations and utilize it as a source of energy. Kochmann and Hall showed that the existence of fasting rabbits may be prolonged through the administration of small amounts of alcohol.

Lewin and also Roger find that the fasting animal possesses a greater tolerance for such alkaloids as quinine, atropine and nicotine; Jordan, on the contrary, found the tolerance for digitalis diminished, the lethal dose being smaller for starving than for well nourished dogs. The action of the digitalis itself is also modified in some essential details which is probably caused by alterations in the cardiac mechanism. Thus, for instance, in the first phase of the digitalis action the retardation of the heart beat fails to appear which is probably associated with the lessened irritability of the vagus nerve already alluded to.

g. Protective Function of Blood

The question of the resistance to infection of the fasting organism is of no less practical importance. Delafuoy and Bourguignou discovered some years ago a hitching disease in sheep which oc-

curred only among poorly nourished animals. The disease could not be transmitted to sheep in good nutritional state, and the sick animals improved rapidly when their nutrition was properly cared for. Stimulated by this observation, Canalis and Morpurgo experimented with the view of determining the effect of inanition on the susceptibility to infection. They selected for this study the anthrax bacilli, and experimented with pigeons and rats which have a natural immunity against these pathogenic microörganisms. No change was produced in the resistance of the rats, but the behavior of the pigeons was quite different. Of the 12 normal pigeons inoculated with the anthrax organisms only two died. If, however, the pigeons were subjected to fasting immediately after the inoculation, or if at the time of the inoculation they had already fasted a few days, the disease invariably developed and the pigeons died. Of 16 fasting birds infected with anthrax 15 died within two to seven days after the inoculation. Feeding restored to the pigeons their lost immunity, unless the inanition already extended for eight or nine days; in other words, in the most advanced inanition period, when the organism suffers serious pathological changes, there is no longer any possibility of saving them by feeding.

These results were substantiated later by London who added also the interesting observation that in the starving birds the anthrax bacilli appeared in the blood on the second day following the inoculation. Furthermore, the immunity is destroyed not only when the pigeons are subjected to complete inanition, but even when the diet necessary to maintain a stable body weight is reduced to one-fourth the pigeons lose their insusceptibility. The remarkable thing is that, as was shown by London, a reduction of the diet to one-third is not followed by similar untoward consequences, although the difference in the actual quantity of food is very insignificant (i. e., 2 gms. of peas less per day). The lack of water is by far the more potent factor in bringing about the loss of immunity. With plenty of water even one-fifth of the solid food (peas) is sufficient to insure resistance to infection; on the other hand, the full ration of peas supplemented with an insufficient quantity of water will have just the opposite effect. It is possible that the diminished resistance to the disease is due to the altered morphological condition of the blood, though there is no valid evidence to establish this point.

An important factor in exposing the organism to infection is

the increased permeability of the epithelial lining of the digestive tract, as was shown by Ficker. His experiments demonstrate the ready penetration of tissues by microörganisms during inanition and throw light on a number of phenomena occurring in the fasting organism. Ficker found in fasting animals (rabbits, dogs, cats, mice, rats) a regular migration of bacteria from the alimentary canal into the tissues by way of the lymph and blood stream, and this is true of the bacteria indigenous to the digestive tract or those which have been experimentally introduced. The moment when this migration begins depends apparently on the stage of inanition. In rabbits this takes place usually after three days, in dogs after about 15 days of fasting; i.e., in either case at the close of the second or at the beginning of the third inanition period. At that stage the invasion of the organism by bacteria from the intestinal tract may be demonstrated. The migration of leucocytes into the walls of the intestines, which will be discussed in the next chapter, and the loss of the mobile elements from the spleen at the close of the second inanition period referred to in an earlier connection (see p. 95) are all apparently correlated phenomena. The same condition has been observed in the hibernating animals; in other words, this occurrence is common to both physiological and experimental inanition.

The migration of bacteria into the blood stream of fasting organisms is regulated by the degree of starvation. Thus, in the dog Ficker found the migration to commence not before the animal had fasted about a fortnight. This may help to explain why Meltzer and Norris obtained negative results with blood from fasting dogs inoculated with typhoid bacilli. These investigators cultured the blood from dogs which fasted only five days. It may be well, therefore, to repeat their experiments and to study the bactericidal action of the blood of inoculated animals at different phases of their inanition, which can be determined by the loss in body weight.

According to Ficker the agglutinating power of the serum of fasting rabbits is not affected.

Inanition is apparently not a predisposing factor in anaphylaxis. Konstansoff sensitized guinea pigs with various proteins and found that in a state of inanition the animals were resistant even to doses many times greater than the fatal injection. The resistance is proportional to the degree of starvation, and at a

certain advanced phase of inanition anaphylactic shock fails to appear altogether.

According to Konstansoff the complement content decreases during inanition.

Bizzozero showed that hemolysins developed in chickens by immunization with sheep's red blood cells are not affected by absolute inanition, and he regards this fact as proof that the hemolytic and bacteriolytic power of the organism are entirely distinct phenomena.

Zilva studying the influence of various deficient diets on the production of agglutinins, complement and amboceptor found that guinea pigs fed on a quantitatively restricted but mixed diet as well as on a scorbutic diet showed no differentiation from those receiving an unrestricted mixed diet.

A subject still very imperfectly known but one which merits a most careful investigation is the *increase* in resistance to infection revealed by organisms which are recovering from inanition. Roger and Josué report such an increased tolerance towards *Bacilli coli* in rabbits which had undergone a preliminary fast of five to seven days. The inoculation with the bacterial culture took place three to eleven days after the fast was broken. In each case the control rabbits succumbed to the infection, while all the rabbits which had previously fasted survived the inoculation. These experiments, however, need verification.

h. Glandular Activity

Although inanition is a condition of the organism wherein the cessation of digestion is the most obvious result, yet neither the rhythmic movements of the alimentary tract nor the glandular activity stop at any time during fasting.

Carlson in his study of the stomach contractions in a man who fasted two weeks found that the decrease in intensity of hunger sensation was not due to a decrease in intensity of gastric hunger contractions, but to cerebral depression and asthenia of the stomach. Rogers working in Carlson's laboratory observed an increased tonus of the stomach musculature in fasting rabbits; Patterson records similar observations in starving dogs. In the fasting dog the hunger contraction persists in spite of the fact that the hunger sensation is depressed, and in the extreme stages

of starvation the contractions become even more prolonged and almost tetanic in character.

The secretion of saliva diminishes greatly, and according to Barbèra Succi on his seventh fast day secreted for three hours no more saliva than he did ordinarily in five minutes. The decrease in salivary secretion is not due to failure of the nervous mechanism which controls secretion. In fasting dogs, even in an advanced stage of inanition, the submaxillary can be excited to activity through chorda tympani stimulation, the latent period being even shorter than in the normal dog. The saliva thus obtained, though less in amount than normally, showed no qualitative differences. The mechanism of reflex secretion is likewise apparently intact since an augmented secretion of a clear and watery saliva is called forth by introducing acetic acid into the buccal cavity.

The secretion is affected by injections of pilocarpine and atropine in the same manner as in well fed dogs, the one exciting, and the other inhibiting it; under the atropine action chorda tympani stimulation fails to cause a flow of saliva.

The chorda tympani secretory fibers supplying the submaxillary gland retain their excitability to the very last moment of the animal's existence; stimulation of the cervical sympathetic fibers, on the contrary, fails to provoke any secretion.

The gastric juice secretion is likewise continuous throughout inanition. Whether with the prolongation of the fast there is a hypersecretion or a hyposecretion of juice, as is claimed by different observers, does not need to be considered here as it seems very probable that such differences are not of fundamental importance, being caused by special conditions.

Barbèra studied gastric secretion in dogs with "Pavlov stomachs." The juice was collected from the miniature pouch while the peripheral stump of the resected vagus was stimulated with induction shocks (60 to 70 per min.). The juice gained by this method from dogs, which lost even as much as 35 per cent of their weight through starvation, was found to contain very little free acid and had a weak enzymatic power as shown by its digestion of albumin to the peptone stage. It seems therefore likely that the gastric glands retain their secretory function even through the advanced stages of inanition, the nervous mechanism controlling the glandular activity being likewise intact. Whatever changes Barbèra did find were primarily quantitative in nature.

Rütimeyer in a young woman who fasted 24 days found the total and free acidity of the stomach contents much reduced at the end of the experiment, though the peptic digestic power (Mett's tubes) was only slightly affected.

Tangl determined the hydrogen ion concentration of the stomach contents in a fasting man, and records variations in the H-ion concentration from 0.016 to 0.085 gram equivalent per liter, which corresponds to 0.06 to 0.33 per cent of free hydrochloric acid.

Carlson in a subject who fasted 15 days observed that the gastric secretion was continuous all through the period of abstinence.

Similarly, the tryptic activity of the pancreatic juice is not lost in inanition. Carvallo et Pachon working with glycerine extracts from pancreas of well fed and starved dogs demonstrated that both contained trypsin. Wertheimer and also Barbèra show that prolonged fasting does not abolish completely the irritability of the pancreatic cells, which may be made to secrete in response to acid introduced into the duodenum. The pancreatic juice thus obtained hydrolyzes protein and can also convert starch to glucose, but its action is much weaker than that of the juice taken from a well nourished animal. Even in dogs which lost 45 per cent of their weight as a result of inanition Barbèra found the pancreatic juice to possess proteolytic power, while the enterokinase content of the small intestine differed little from that of normal dogs.

The secretion of bile in the fasting animal has been more thoroughly investigated from a strictly quantitative standpoint. Lukjanov examined the bile obtained through fistula in guinea pigs, both normal and those which lost various proportions of their body weight through fasting. The amounts secreted per hour in the different conditions is tabulated below:

Period	*Grams of Bile Secreted in One Hour*		
	Per Kilogram of Body Weight	*Per Ten Grams of Liver*	*Change in Per Cent*
Normal	9.3006	2.7523	...
Inanition Period I	9.5023	3.1500	+2.2
Inanition Period II	7.5552	2.2301	—18.8
Inanition Period III	7.5259	2.2152	—19.1
Inanition Period IV	5.5729	1.5364	—40.1

The bile secretion in the first inanition period is somewhat greater than in the normal guinea pig (+2.2%), this being due to the fact that the bile becomes more fluid and contains a higher percentage of water. In the next two periods the secretion, though much less than in the fed animals (— 18.8% to 19.1%), remains constant and only in the last, or fourth period of inanition a further abrupt diminution (— 40.1%) in bile secretion occurs. We see here, therefore, a new demonstration of the truth that the course of inanition falls naturally into four distinct phases, the second and third of which represent a condition of physiological equilibrium and stability at a low plane.

The bile of the fasting animal is somewhat poorer in mucin, but contains a higher percentage of substances soluble in alcohol and in ether. The chief alteration in the secretion of bile occasioned by inanition is quantitative.

The secretion of milk differs from ordinary glandular activity in that the mammary glands, which are active only intermittently, elaborate their product from nourishment brought to them by the blood and lymph. The product of their activity (the milk), however, serves no purpose in the mother's organism, being a drain upon its resources even while the organism is well supplied with nourishment. It is not surprising therefore that the secretion of milk is affected very readily both quantitatively and qualitatively whenever the mother's nutrition is defective.

Barbèra studied experimentally this problem of the influence on milk secretion of complete fasting. The quantity of the milk diminished continuously with the progress of the fast, being only one-seventh of the normal amount after 14 days of inanition. The milk itself became poorer in water, protein, sugar and inorganic salts, though the fat content remained unchanged. Lusk in fasting goats found an increased fat content of the milk, though the total quantity of secreted milk was greatly reduced.

These results are also corroborated by later investigations on the effect of various adverse conditions of feeding and undernourishment on the composition of cow's milk. Rühle [1] as well as Weidemann und Singer [2] found no evidence of a decrease in the fat content of the milk, though the volume of milk and the percentage of solids exclusive of fat were reduced under the circumstances of the experiments.

[1] *Ztschr. Nahr. Genussm.*, 38, 277, 1919.
[2] *Ibid.*, 39, 130, 1920.

In the war-ravaged part of Europe it is reported that the underfed and half-famished mothers were unable to nurse their babies, because their emaciated organisms could not supply the mammary glands with the necessary materials for the production of milk. Even where the mothers were able to nurse, the infants still failed to thrive on this diet. Kauppe examined the milk of a large number of nursing women and finding the fat content practically normal concluded that the failure of the babies to grow properly was the result of psychic influences generated by war-time anxiety. From Barbèra's results, however, it is clear that the fat content is the least reliable index of the changes which fasting produces in milk. Besides, there is no need to resort to such fanciful interpretations as psychic influences, when we know that the milk of starved or undernourished mothers probably lacks those imponderable components which ordinary chemical analysis cannot reveal (McCollum), but which are nevertheless absolutely indispensable for the normal growth of the child.

Allessandro finds that the secretion of tears diminishes gradually in the course of inanition.

i. Absorption and Assimilation

It may be objected that it is not proper to consider the question of absorption and assimilation in this connection, since inanition is a state of the organism in which neither of these functions is being exercised. But inanition undoubtedly affects these functions, and this becomes manifest as soon as the fast is broken.

I found in experiments with trout that after two weeks of inanition the absorption of fat is seriously impaired. The utilization of the fat of the food diminished from 94.2 to 91.7 per cent, and the feces were unusually fatty. Whether this resulted from a lack of lipolytic enzyme, or was due to a disturbance in the absorption mechanism could not be definitely determined at the time. The fact that the glandular activity has been shown to be generally very little affected by fasting makes the latter assumption more probable.

The "hunger diabetes" of Hofmeister is another very striking phenomenon accompanying inanition. He found that in dogs even after a brief fast the administration of starch powder leads

to a quick onset of glycosuria which appears one to two hours after feeding and may last as long as four hours, and as much as 30 per cent of the starch is recovered from the urine as sugar. The defective assimilation of the sugar is due to a lowering of the tolerance, thus resembling the condition in mild diabetes, and hence was named by Hofmeister "hunger diabetes." The condition is not known to occur in other animals and cannot therefore be regarded as a typical inanition effect. It does not occur in man, though in babies a brief fast commonly brings on a similar diminution in the ability to assimilate sugar (Rietsch) which appears in the urine.

Allen experimenting with partially depancreatized dogs corroborates Hofmeister's discovery but shows that this in no way contradicts the well established phenomenon of an increased sugar tolerance following a fast. He says:

"Hofmeister's work is confirmed in these (partly depancreatized) dogs much more strikingly than in normal dogs, and heavy glycosuria often occurs on feeding bread either alone or with sugar. The same phenomenon has frequently been witnessed in dogs changed suddenly from a protein or fat diet to a carbohydrate diet. But no matter how heavy the glycosuria, it is transitory just as in Hofmeister's normal dogs, and it has never been possible to produce diabetes thus in any animal which was non-diabetic on the same diet before the fast. The phenomenon seems to illustrate some state of unpreparedness of the body for the unaccustomed carbohydrate flood, but it does not represent any true diabetic tendency or any exception to the general rule that the pancreatic function is strengthened by fasting."[1]

[1] *J. exp. Med.*, 31, 575–586, 1920.

CHAPTER IV

MORPHOLOGICAL PHENOMENA IN INANITION

a. Cellular Changes

The morphological picture presented by tissues of hibernating organisms is dominated by their general state of quiescence under which, according to Monti, cell proliferation practically ceases. Not so in the case of experimental inanition. In tissues of starved animals cell division may continue sometimes even through the advanced stages of inanition. Hofmeister observed mitoses in the epithelium of the digestive tract of fasting cats, and similar observations have been made by Bizzozero and by Morpurgo. Retzius also noted that cell division becomes less frequent during inanition but does not cease altogether. Rabl found many mitoses in the epidermis and tongue glands of *Salamandra atra* which starved 5 to 7 months. This is corroborated by the observations which Morgulis made on starved fresh water newts. When feeding is resumed after a preliminary period of fasting a much augmented mitotic activity ensues invariably and promptly. Morpurgo's studies on puppies give a good demonstration of this phenomenon since he has shown that in puppies which fasted a few days the number of mitotic divisions is greatly in excess of that found in puppies of the same age but without the experience of inanition. In the fresh water newt, *Diemyctylus,* Morgulis found that feeding after a preliminary period of starvation is certain to produce a crop of mitotic divisions. Nusbaum and Oxner state that the epithelial lining of the intestine of starving nemertines is being worn off and continually replaced by new cells. Moreover, the regenerative power of an organism is not much affected in inanition so that even the much emaciated organism will draw upon its scanty tissue reserves to replace a lost portion (Morgan, Child, Morgulis).

The influence of inanition on the individual cell is very

definite and is revealed already in the early stages by a more or less appreciable reduction in size. This diminution is most readily observed in cells of the glandular organs. Morpurgo was among the first to study this problem from the quantitative standpoint. He found that in starved pigeons the volume of the liver cell was only 12,300 cubic micra, or 48 per cent of the also noted that in starved pigeons the nuclei of the liver cells are smaller. Lukjanov investigated the change in size of hepatic and renal nuclei of starved rats. Those which lost 29.4 per cent of their weight (starved 85 hrs.) had liver nuclei only half the size of the normal rat (213 instead of 426 cubic micra). The renal nuclei, however, lost only 23 per cent of their normal volume.

Measurements extending to both cells and nuclei are not numerous yet the behavior of the cell-nuclear complex in inanition deserves particular attention. This problem of the relationship between nucleus and cell body under the influence of inanition has been studied by Morgulis in various organs of fresh water newts.

The liver cell of a normal salamander has a volume of approximately 23,400 cubic micra (a cubic micron = 0.000,000,001 cubic millimeter) and its nucleus about 1,190 cubic micra. In other words, the nucleus is practically spherical in shape. In salamanders which starved one month the average volume of the liver cell was only 12,300 cubic micra, or 48 per cent of the normal volume; the nuclei measured 590 cubic micra, or 50.4 per cent of the normal. Furthermore, as the ratio between the two main axes indicates, the nucleus has elongated somewhat and thus changed its shape from spherical to elliptical. This is also corroborated by Statkewitsch's observations on liver nuclei of a large number of mammals. The relation of the nucleus to the cell body, however, remains essentially as it was in the normal animal. After two months of fasting the cell volume was only 6,030 cubic micra, or scarcely more than one-fourth of the normal, but the nucleus has undergone no further diminution so that the cell nucleus relation has become radically altered, the nucleus now occupying one-tenth of the total volume. In other words, after two months of starvation the liver cell, though greatly reduced in bulk, had a nucleus twice as large relatively as in the normal salamander. After three months of starvation the walls of the hepatic cells thin out to the vanishing point,

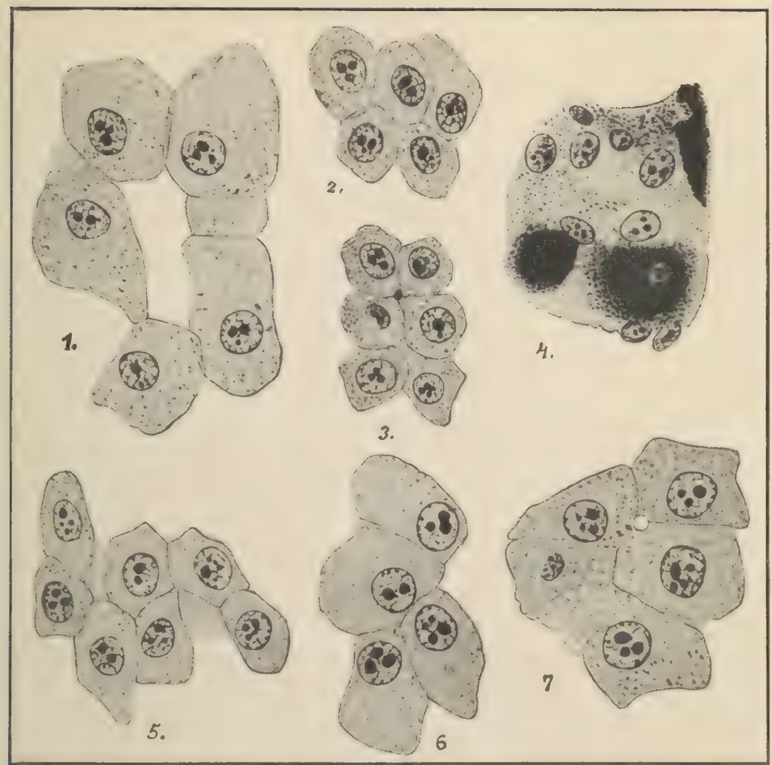

Figure 8.—Groups of cells from livers of normal salamanders (1) and from salamanders which starved for one (2), two (3) and three (4) months. The groups of cells (5, 6 and 7) are from livers of salamanders which were fed on raw meat four, eight, and fourteen days respectively following a preliminary fast of three and one-half months' duration. (After S. Morgulis.)

making it impossible to recognize the cellular boundaries, and over large areas the walls disappear entirely, leaving a syncitium or fused mass of protoplasm with nuclei scattered through it. Estimating, therefore, the mass of protoplasm belonging to each nucleus the volume of the cell is found to have been reduced to one-sixth of the normal. The nucleus has likewise somewhat diminished, but it still constitutes about one-tenth of the cell body.

Reviewing the results obtained with the liver cells, two things must be emphasized: first, that the loss sustained by both cell body and by nucleus is not proportional to the loss in body weight. Even after four months of starvation the loss of the entire organism is about 50 per cent, whereas the reduction in volume of the liver cell is 52 per cent in one month, 74 in two months and 80 to 85 in three months of fasting. The other point which deserves mention is that while the cell body decreases continuously the nucleus attains a minimum volume at a relatively early stage after which it is subject to very little further change. Correspondingly, the 1: 20 ratio between nucleus and cell body soon becomes approximately 1: 10, which is maintained more or less throughout the later phases of inanition. It is also to be pointed out that the nuclei instead of remaining spherical tend to become elongated.

The epithelial cells from the intestine of a normal salamander are large and narrow with a broad rim of cilia at the free end. The ratio between the height and width of these cells is 2.8: 1, so that the average normal cell is about three times as long as it is wide and occupies a volume of approximately 26,000 cubic micra. The nucleus, of course, is oval, the ratio between its long and short diameter being 1.73: 1; it occupies about one-fifteenth of the entire cell volume. During inanition the volume of the intestinal epithelial cells diminishes rapidly. Already after one month of starvation the volume of the cell is only about 10,000 cubic micra, and the nucleus is also smaller but owing to its slower rate of reduction it now constitutes one-tenth of the total volume. The shape of the cell remains unaltered, the ratio between height and width being the same as in the normal cell. The nucleus, on the contrary, undergoes a change in size and shape. The ratio between the two diameters becomes 1.96: 1, showing that the nucleus is much more elongated now than it was in the normal salamander. In the more advanced stages of

starvation the cells grow still smaller, tending to diminish in width more than in length so that the cells become at the same time narrower. The volume of the epithelial cell after one month of starvation is about 60 per cent less than normal; after two months 70 per cent, and after three months about 85 per cent. The reduction in size of the epithelial cells of the intestine runs, therefore, parallel to that of the liver cells. The ratio between nucleus and cell body changes continually, and after three months of starvation the nucleus occupies somewhat less than one-fifth of the entire volume. The nucleus, however, does not change shape but retains the elongated form which it assumed at an earlier stage. In the first month of starvation it has lost about two-thirds of its volume and its shape changed in a striking manner, but with further prolongation of the fast it tenaciously keeps its shape while continuing to diminish in size slowly.

Similar observations have been made on pancreatic cells. In the normal salamander these have a volume of about 7,600 cubic micra and their nucleus about 740 cubic micra. The latter is slightly ellipsoidal, the ratio between its principal axes being 1.13: 1. The nucleus, therefore, occupies approximately a tenth of the entire cell. By the end of the first month of starvation the cell body loses 36.4 per cent of its original volume while the nucleus decreases 19.4 per cent. The pancreatic cell, therefore, diminishes less than either the liver cell or the epithelial cell from the intestine. The nucleus shows no appreciable change in shape and constitutes now one-eighth of the entire cell because it diminishes slower than the rest of the cell body. As the inanition continues the cell becomes gradually smaller, being less than half the normal size after two months and slightly over one-fourth after three months of starvation. The nucleus as usual decreases at a much slower rate, losing only about a third of its bulk in two or three months of inanition. The ratio between nuclear and cellular volume changes progressively so that after three months the nucleus comes to occupy but little more than a fifth of the total volume; in other words, the nuclei have become, relatively speaking, twice as large as they were in the normal pancreatic cell.

The figures represent a series of different cells drawn with the aid of a *camera lucida* under the same magnification of the microscope. They are typical cells found in normal salamanders

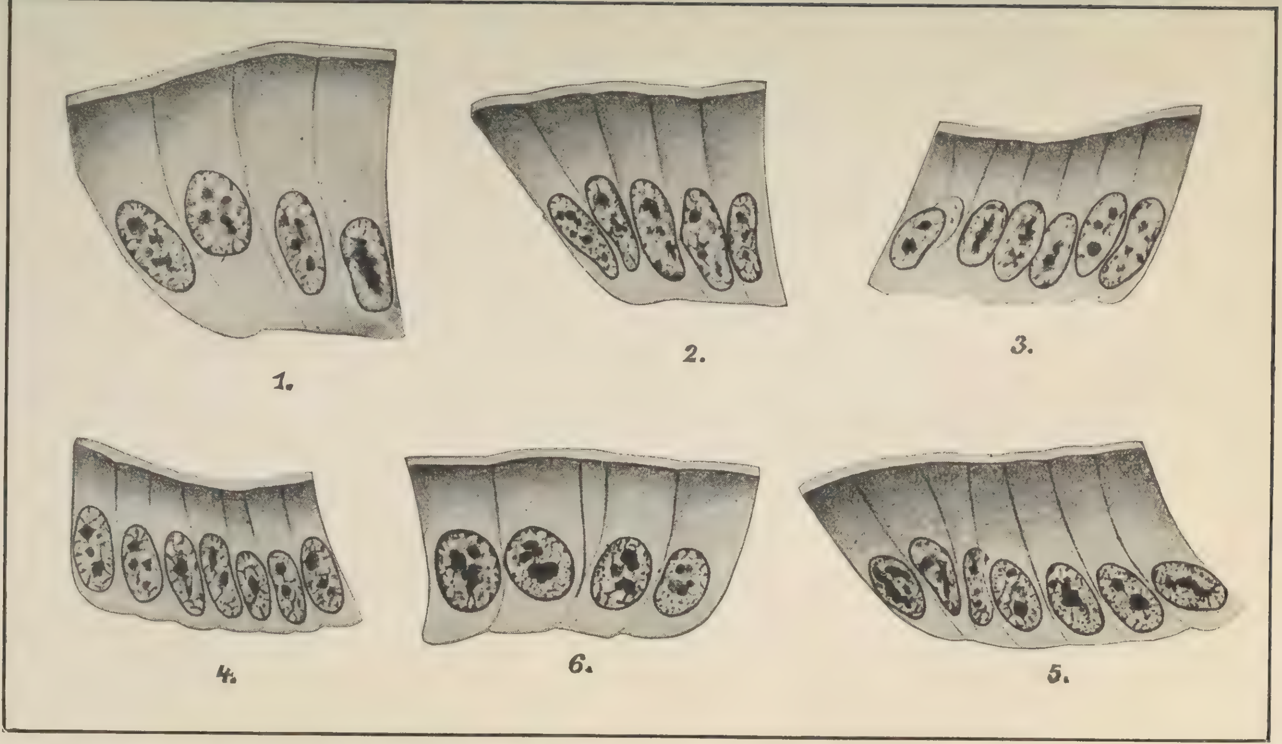

FIGURE 9.—Groups of cells from the epithelial lining of the duodenum of normal salamanders (1) and from salamanders which starved one (2), two (3) and three (4) months. The groups of cells (5 and 6) are from salamanders which were fed on raw meat four and eight days respectively, following a preliminary fast of three and one-half months' duration. (After S. Morgulis.)

and in those which starved one to three months. Furthermore, the recuperation of the cells is shown when the animals are nourished again after having fasted for three and a half months. The regeneration of the cells is marvellously rapid, the original normal condition being practically restored after 14 days of feeding.

It may be well to consider in this connection the cellular growth following upon the resumption of feeding. By the end of four days of feeding both cells and nuclei of the liver have gained 34 and 31 per cent respectively, the cell-nucleus ratio, of course, remaining the same. In another four days (i.e., after eight days of feeding) the cell body has already more than doubled in volume (increased 143 per cent) while that of the nucleus increased only 66 per cent, the normal cell-nuclear ratio thus tending to be reëstablished. After fourteen days of feeding the nuclei have already attained normal dimensions again though the cells have not yet reached their normal size. It should be mentioned also that already after the first four days of feeding the nucleus becomes once more spherical. The change in shape, the most immediate effect of which is the reduction in the surface of contact with the cell body, coincides with an abundant inflow of nutrient material and is contrary to that which occurs when under inanition the amount of nutriment in the cellular juices is much diminished. In either case, however, the alteration in the extent of the absorbing surface leads to an establishment of a definite relationship between the cell body and its nucleus.

The duodenal epithelial cells increase even more rapidly. After the first four days of feeding the volume of the cell and nucleus increases 45 and 24 per cent respectively. The nucleus in the meantime assumes its normal shape. By the end of eight days the cell volume has increased almost four times. At the same time both the cell and the nucleus tend to expand, the cell becoming wider and the nucleus more round than they have been originally. At the end of 14 days both cell and nucleus have practically regained normal dimensions; furthermore, the nucleus is again normal in shape and its ratio to the entire cell body is once more reëstablished.

The same holds true for the regeneration of the pancreatic cells except for the minor details of the process.

An examination of the cells and nuclei of albino rats stunted

through chronic underfeeding leads to somewhat different conclusions. The average liver cell of the normal rat (aged 110 days) had a volume of 5,075 cubic micra with the nucleus occupying 247 cubic micra. In two stunted rats of the same age but weighing one-half and one-third of the normal the cellular volume was 3,752 and 3,981 cubic micra and the nuclear volume was 226 and 195 cubic micra respectively. The pancreatic cell of the normal rat measured 1,829 cubic micra, while in the two stunted rats these measured on the average 1,346 and 955 cubic micra. The volumes of the pancreatic nuclei of the stunted rats were 65 and 59 cubic micra, that of the normal rat occupying 94 cubic micra. The reduction in volume of both cell and nucleus does not keep pace with the diminution of the total body weight. Besides, the nuclei showed no tendency to elongate as in the case of the acutely starving salamanders, nor to form a larger proportion of the cell body. These differences may possibly be accounted for by the fact that in our rats which have been stunted in their growth the cell and nucleus were equally hindered in their development.

Mention should also be given to Jarotsky's study of the pancreas cells of starved mice. When his mice suffered a loss in weight of over 30 per cent the volume of the pancreatic nuclei decreased 23 per cent (from 87 to 67 cubic micra) while the longest dimension of the cell changed from 17.9 to 13.6 micra and the shortest dimension from 13.8 to 11.5 micra.

The facts bearing upon the cell-nucleus relationship are important in considering the problem of cell division. It was pointed out how mitosis is greatly promoted by preliminary inanition. Gerassimov demonstrated that the size of the cell of the plant Spirogyra is a function of its nuclear mass, enlargement of the nucleus stimulating the cell to further growth. This idea found also corroboration in Boveri's discovery that sea-urchin eggs vary in size directly with the number of chromosomes they contain. Hertwig supposed that the change in relation between cell body and nucleus furnishes the needed stimulus to cell division. In our inanition experiments we witness that the cell-nucleus ratio is not fixed but changes according to the vicissitudes of the organism's existence. The intensive process of cell division when feeding is resumed coincides with a condition when the nuclei have actually become too large for the cell body, not too small as would be expected on Hertwig's hypothesis. The

inanition experiments emphasize that a stimulus, which in this case is probably nutritive in nature, is necessary to start the mitotic process.

It is interesting to compare the behavior of the nuclei under experimental and under physiological inanition. Leonard observed in hibernating frogs that the size of the liver nuclei is in inverse relation to the size of the cells, being largest during the hibernating period and decreasing to a minimum size in the summer when the cells have reached their greatest dimensions. In physiological inanition the nucleus becomes *actually* larger unquestionably at the expense of the cell substance; in experimental inanition both cell and nucleus diminish but at different rates so that the nucleus soon becomes *relatively* larger than under normal circumstances.

The quantitative data obtained from this study of the changes in cells and nuclei furnish evidence that the nucleus exercises a controlling influence over the cell and that, therefore, the loss sustained by the different tissues and organs is ultimately regulated by the nuclei. This is brought out by our results obtained with the fresh water newts, *Diemyctylus vir.*, tabulated below:

Organ	*Initial Volume of Nucleus*	*Diminution of Volume in Per Cent*		*Duration of Fast*
		Nucleus	*Cell*	
Pancreas	740 c. micra	19	36	One month
		37	56	Two "
		35	71	Three "
Liver	1190 c. micra	50	50	One month
		50	74	Two "
		60	81	Three "
Duodenum ..	1800 c. micra	41	62	One month
		48	69	Two "
		56	83	Three "

The pancreas cell having the smallest nucleus suffers the smallest relative reduction, while the epithelial cell from the duodenum having the largest nucleus sustains also the largest loss.

Miss Allescher showed likewise that the rate of loss in volume of different starving infusoria is directly proportional to the surface of contact between nucleus and cell body.

Organism	*Percentage Loss in Volume*			
	8° C.	*15° C.*	*25° C.*	*30° C.*
Dileptus	56	97	98	99
Stentor	32	54	76	..
Paramecium ..	28	49	58	..

Miss Allescher's results are very important demonstrating as they do the fundamental phenomenon of the control of the cell by the nucleus. They show this even more strikingly than our own studies of the tissues of higher animals, namely that infusoria possessing a compact nucleus (*Paramecium*) lose much less in volume as compared to those having a subdivided nucleus (*Dileptus*) which, at the higher temperatures, may become reduced to one per cent of their original volume.

b. Effect on Unicellular Organisms

The effect of inanition on the unicellular organisms is very profound so far as the morphological condition is concerned and offers many points of similarity with the changes seen in the tissues of multicellular organisms. Sosnowsky found that *Stentors* when deprived of food will still go through two or three divisions but as the inanition is prolonged their nuclei become irregular and vacuolated and frequently break up into fragments; the animal itself assumes various peculiar shapes and finally dies. Borowsky found that *Actinospherium* resists inanition 14 to 18 days. The nuclei become fewer in number which is believed to be due to fusion inasmuch as the individual nuclei are appreciably larger than in normal organisms. This fusion of nuclei by reducing the surface of contact probably slows up the rate of loss of the entire cell. In advanced stages the protoplasm becomes extremely vacuolated.

The most thorough investigation of the influence of inanition on infusoria was made by Wallengren who experimented with both *Paramecium* and *Colpidium*. The cytological effect of the starvation does not appear until the reserve food contained in the vacuoles is completely used up when apparently a demand upon the organism's own substance is made. *Paramecia* can survive inanition at least 14 days. The first external signs of emaciation

—elongation of the body and increased transparency—do not appear, however, until the third day of inanition. Vacuolization of the protoplasm, which is the most important degenerative effect, does not commence until about the ninth day. It may be said, therefore, that the morphological integrity of the organism is retained during two-thirds of the starvation period. Considering that the vacuolization is at first mild in character it seems entirely probable that during the larger part of the inanition the organism is morphologically normal in the same sense as it retains its physiological integrity. About the fourteenth day of fasting, however, the vacuolization of the protoplasm is already so far advanced that many of the infusoria begin to disintegrate and die. Schaudinn in 1899 (Abh. K. Akad. Wiss., Berlin) recorded similar observations in experiments with *Trichospherium*—first of all the protoplasmic inclusions disappear, then the vacuolization of the protoplasm ensues leading ultimately (in about three weeks) to complete disruption of the organism.

Taking Wallengren's measurements of the changes in length and width of the *Paramecia* as a clue to the loss of body substance, one is justified in estimating this loss at the time vacuolization becomes extensive as being over 40 per cent.

The diminution in size and the increase in transparency of the infusorian organism are both due to the fact that the endoplasmic granules are used up. The ectoplasm, or outer layer of the organism, shows no visible effects in the early stages of the inanition, but after 10 days of starvation, i.e., when according to our estimate the organism lost about 40 per cent and the endoplasm is already much vacuolated, the ectoplasm is also encroached upon. It becomes progressively thinner, loses the cilia while the trichocysts deprived of their support are drawn into the body and are absorbed there. A similar gradual absorption of the external layer has likewise been noted by Borowsky in *Actinospherium.*

The behavior of the macronucleus and of the micronucleus deserves special attention. The former shows considerable changes (granulation, vacuolization) after four days of starvation. It finally breaks up into fragments and serves as nutriment for the rest of the organism. The micronucleus, on the contrary, betrays no signs of degenerative changes all through the inanition. It persists retaining apparently its normal character together with

the pulsating vacuole which diminishes but does not stop acting. The two perform, therefore, functions which are indispensable to the continued existence of the organism.

If granular decomposition of the protoplasm and vacuolization have not gone very far, resumption of feeding leads to rapid disappearance of the vacuoles and the body is restored to its normal dimensions within about three days. New cilia and trichocysts are regenerated but the deeper cytological effects of the starvation wear off more slowly. If, however, the degenerative alterations have advanced too far the organism can no longer be saved.

The preservation of the micronucleus in starving infusoria and the important rôle which it comes to play later in the recuperative process stimulated by the renewal of feeding brings us face to face with one of the fundamental problems in the general physiology of inanition. The contrast in the behavior of the two nuclei—the macronucleus dissolving relatively early in inanition—the different manner in which the ectoderm and the endoderm are both affected, the persistence of the pulsating vacuole—all these facts argue unmistakably that even in the unicellular organism some structures resist the effect of inanition more vigorously than others. These structures are essential to the continuance of the organism's existence and they maintain their integrity at the expense of the less resistant ones. It is not necessary to assume that the preservation of the organs which apparently have the power to regulate the metabolism of the cell is in obedience to some purposeful or teleological object as superficial consideration of the facts might suggest. There is a struggle between the different parts of the cellular structure for the scanty supply of available nutriment. All parts of the organism undergo reduction, but not all are equally efficient in attracting nourishment. The processes of oxidation are particularly intense around the nucleus and this may account for there being more nourishment available, just as in the higher organisms the greater flow of blood through the more active organs insures them a more liberal supply of nutriment.

c. Effect on Low Organisms

In organisms higher in the evolutionary scale, where the functional differentiation of various parts is more definite, we see

more striking results of this uneven response to inanition. Stoppenbrink's figure of a starved planarian demonstrates this beautifully.

The worms which in consequence of starvation were reduced to one-thirteenth normal size possess an entirely different shape because the anterior part containing the cerebral ganglia and eyes has been reduced much less than the posterior part. Such alteration in the form of the body can also be seen in the more highly developed organisms. Thus, in the fresh water newt

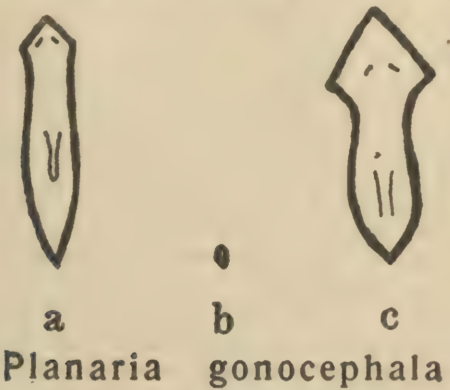

FIGURE 10.—A normal (a) and a starved (b) planarian. The starved worm was reduced to 1/13th of its original size. The latter is also shown magnified 13 times (c) to make it comparable with the normal animal. This figure shows the striking alteration in the relative proportions of the organism resulting from the different degree of involvement in the inanition reduction of the different parts of the body. (After Stoppenbrink.)

inanition causes a greater shortening of the tail than of the trunk so that starved salamanders are short-tailed. Hatai in his study of the effect of insufficient food on growing albino rats likewise observed that the most conspicuous external difference between normal and stunted animals was the changed ratio between body length and tail length, the stunted rats being short-tailed.

These gross morphological manifestations of the influence of inanition find their counterpart in more fundamental differences of the behavior of various tissues. The latter are so fundamental in character that the essential facts can be learned even in the most lowly organized animals. Thus, Nusbaum and Oxner's

histological study of starving *nemertines* shows clearly that the nervous system represents the most resistant tissue. Muscles, though they atrophy considerably, do not, however, undergo degeneration except in very protracted starvation (one year). Epithelial tissue is much more affected than muscle.

Disregarding the atrophy of the cell and nucleus, little of any consequence happens histologically before we reach the advanced stages of inanition. But before discussing these in detail we will consider first some cytological phenomena which occur almost immediately. The earliest effect of inanition is the appearance of histologically demonstrable fat globules in various cells. Traina has shown that the presence of such globules is a physiological phenomenon, the lipoid material being an integral part of the protoplasm. Soon after fasting begins, however, this lipoid material becomes easily demonstrable where under ordinary conditions it could not be shown by staining methods. The fact that these fat globules appear at the very commencement of inanition disposes of the supposition that this is due to a degenerative process. Neither is there any reason for assuming with Nikolaides that these fat granules owe their origin to a transformation of albumin of the protoplasm. The important thing generally overlooked in this connection is that protoplasm holds such a large quantity of fat because of its colloidal nature. Protoplasm is an emulsion of protein, fat and carbohydrate, and the latter plays an important rôle in stabilizing the emulsion and preventing it from breaking up easily. When, however, as always happens in inanition, the carbohydrate moiety of the protoplasm is quickly metabolized the stability of the fat-protein emulsion is likewise impaired and the fat commences to separate out in the form of minute particles. Later, as the carbohydrate is still further used up, the particles enlarge and coalesce into coarse globules producing such changes in the microscopical picture which Cessa-Bianchi's figures of liver and kidney cells of fasting animals readily reveal.

Passing now to the microscopical picture presented by the tissues of organisms under more prolonged starvation one is more impressed with the fewness of these changes than with the degree of actual change. It is rather difficult to give a comprehensive view of the morphological alterations but phenomena of general significance will be specially emphasized. The study of the morphological changes will concern itself chiefly with the more

advanced stages of inanition since the early changes are physiological and not pathological in character.

d. Changes in Blood

The blood being made up of mobile cellular elements derived from different sources and possessing a limited span of existence it is, of course, natural to expect a considerable rearrangement in its morphological composition during inanition. Indeed, the blood is practically the only tissue where progressive changes can be recognized which begin in the earliest stage of the fast. The number of erythrocytes may temporarily increase during the first inanition period as in the case of Ljubomudrov's dogs. But this preliminary increase is not found invariably and the possibility is likewise not excluded that it is not associated with a slight condensation of the blood. In fact, dogs fasting without any water (Poletaev's dogs) show an increase in the number of red cells until a much later stage (loss = 30%). But even in this case the number of erythrocytes ultimately begins to decrease and continues to do so until the animal dies. Little change has been found in the blood count of human fasters. Levanzin's red count, though fluctuating very much from day to day, was essentially the same on the thirty-first fast day as it was when the fast just began, and Tauszk studying Succi's blood also found that the count remained unchanged during the 30 days of his fast.

The effect upon the white blood cells is much more interesting. Perhaps one of the most startling morphological phenomena is the leucopenia appearing early in inanition. The quickness of the onset of the leucopenia shows that this cannot be due to a failure of new cells entering the blood stream but to an emigration of leucocytes into the tissues, and this view receives corroboration from the actual observation of an invasion of certain organs by leucocytes.

Tauszk found in Succi's blood that the ratio of red cells to whites increased gradually from the first to the last fast day, and since the red cell count—as already pointed out—remains the same the white cells must become continuously fewer in number. The ratio was 545:1 on the third day, 744:1 on the second and 1302:1 on the last, or thirtieth, fast day. It must be concluded therefore that the number of leucocytes was reduced to one-third. The relative number of lymphocytes decreased while

that of the eosinophiles and polymorphonuclear leucyocytes increased.

Charteris' report on the differential leucocyte count of Beauté during a 14-day fast also shows a gradual increase in the number of eosinophilic leucocytes.

Ljubomudrov likewise found an increase in the eosinophile count of fasting dogs. It should be noted, however, that the results for the dog are not very consistent. Thus, Howe and Hawk in their study of the differential leucocyte count of fasting dogs observed a gradual increase in the eosinophiles in only one of their dogs while in all the others the eosinophiles seem to have disappeared. Howe and Hawk have found that there is a progressive diminution in the polymorphonuclear leucocytes which is paralleled by an increase in the lymphocytes during fasting. In a dog which fasted 112 days the polymorphonuclear count, after a preliminary rise from the normal level of 52.8 per cent to 68 in the first fast days, gradually dropped off to only 24.8 per cent on the last day of the fast. At the same time, the lymphocytes, after a temporary fall from the normal 41.4 per cent to 28.4 on the first day of fasting, increased rapidly, reaching 76 per cent on the 106th day of fasting, but declined again somewhat and on the last day of fasting was 67.2 per cent. Unfortunately, these authors have not made a total white cell count and have apparently entirely neglected to differentiate between mononuclear leucocytes and lymphocytes.

In an extensive research of the differential leucocyte count in rabbits at various stages of inanition Okintschitz found the following interesting facts regarding their relative distribution:

Period	*Per Cent of Total Count*			
	Lymphocytes	*Mononuclear Leucocytes*	*Eosinophile Leucocytes* *	*Polymorphonuclears*
Normal	25.9	11.6	51.0	11.5
Inanition Period I	24.5	12.7	49.6	13.0
Inanition Period II	16.6	16.3	56.7	10.4
Inanition Period III	16.1	18.8	60.1	4.7
Inanition Period IV	9.0	21.6	66.3	2.6

* The extremely high eosinophile count given by Okintschitz for the rabbit would at first sight suggest that it might be erroneous. I requested, therefore, my assistant, Mr. Jahr, to examine the differential blood count in a number of normal rabbits in our laboratory. Blood smears were prepared from blood obtained from an ear vein and stained by Wright's method. Although the results of his leucocyte counts were variable, the very high eosinophile counts which he obtained dissipate any doubt as to the correctness of Okintschitz' figures. It seems that in the normal rabbit the eosinophiles may form a very large proportion of all the white cells.

It is evident that the morphological make-up of the rabbit blood changes its complexion radically, especially in the advanced stage of the fast. The interesting thing to note is that the number of lymphocytes changes but slightly in the first period, a marked and somewhat abrupt fall occurring in the second period. It should be recalled that Lasarev found that the spleen—one of the important sources of lymphocytes—loses no weight in the first inanition period, undergoing, however, a maximum reduction in the second period. During the middle two periods (II and III) the relative lymphocyte number remains unchanged, but in the fourth, or exhaustion, period a new abrupt falling off in their number can be observed. This new drop is undoubtedly associated with a general state of exhaustion which at this phase of starvation overtakes all the organs including the various lymphatic glands. The increase in the eosinophiles and the decrease in polymorphonuclear cells may be regarded as reciprocal. According to Ehrlich the polymorphonuclear leucocytes are derived from mononuclear. It seems probable, therefore, that though the hematopoietic organs continue delivering new mononuclear cells into the blood these are not being transformed into polymorphonuclear cells. Following a transitory increase in the first period, the number of polymorphs then diminishes almost to the vanishing point. Their all but complete disappearance from the blood may be due to a transformation into eosinophilic cells whose number rises particularly at the time when the polymorphonuclear leucocytes suffer the greatest loss.

These considerations receive additional support from the regenerative process following resumption of feeding. Okintschitz fed rabbits which reached the fourth period of inanition (judged by their loss in weight) and examined their differential blood count

Condition of Rabbit	*Per Cent of Total Count*			
	Lymphocytes	*Mononuclear Leucocytes*	*Eosinophile Leucocytes*	*Polymorphonuclears*
Normal	26.0	10.5	52.2	11.3
Starved (—32.7%).	13.6	20.6	60.3	5.3
Feeding resumed				
20% below normal..	23.9	12.4	53.7	9.9
10% " " ..	25.6	11.2	48.5	14.5
4% " " ..	24.0	9.9	49.3	16.7

several times until the animals regained their original weight. His interesting findings are recorded in full.

Soon after feeding has been resumed and while the animal is still 20 per cent below its original weight three changes in the distribution of the white cells become noticeable: a marked increase of the lymphocytes and of the polymorphs, and a reduction in the number of mononuclear cells. This indicates a renewal of activity on the part of the lymphatic organs and a quick transformation of mononuclear into polymorphonuclear cells owing possibly to an improvement in the oxidative processes. By the time the original body weight is nearly restored the differential count is also almost normal again except that there are relatively too many polymorphs and fewer eosinophilic cells.

The thing of particular significance with regard to the leucopenia of inanition is that while the blood is losing its white cells the mucous membranes of the intestinal canal and the underlying tissues become infested with leucocytes. They occur either singly or in masses. According to Mingazzini (Lavore del Inst. anat. Rome, 58, 1900) in the absence of food leucocytes not merely accumulate in the intestinal wall but actually penetrate the mucous membrane and aggregate in the lumen where they ultimately disintegrate. This migration of leucocytes into the intestinal tract has already been discussed in its relation to physiological inanition (hibernation). The phenomenon doubtless has the same significance in experimental inanition and should be viewed in the light of Ficker's discovery already referred to (p. 192) of an increased permeability of the cell membrane to bacteria under the influence of inanition. Ficker has shown that at about the end of the second inanition period the permeability of the cell wall to bacteria reaches a maximum. The emigration of leucocytes is probably associated with this phenomenon.

e. Bone Marrow

The bone marrow being perhaps the best studied of the hematopoietic organs it is appropriate to consider in this place what changes it undergoes during inanition. It has been pointed out before that the chemical changes of the marrow are most profound. Soltz as well as Roger et Josué from microscopical studies consider these transformations to be mucoid in nature. The fat cells may either diminish in size and assume a stellate

shape or frequently without changing form they become filled with the mucoid substance after all the fat had disappeared. The principal degenerative process observed by Roger et Josué in the bone-marrow cells of starving rabbits was atrophy with vacuolization, though where death actually occurred from inanition the depletion of the marrow was complete, whole areas being at times devoid of cellular structures. Soltz observed extensive migration of erythrocytes from the capillaries into the surrounding tissue where they disintegrated and produced pigment infiltration of the bone marrow. This is corroborated also by Roger et Josué who found masses of yellow pigment in the substance of the marrow.

The blood vessels of the marrow become greatly distended. This is probably due to purely physical causes: as the fat is being used up and replaced by water and the substance of the marrow becomes more gelatinous in consistency less resistance is offered to the internal pressure of the vessels which therefore tend to dilate. Soltz describes the formation of many thromboses in the capillaries and veins, and Meyers also found in a man who died from starvation that the capillaries of the bone marrow were greatly engorged with blood.

In the discussion of the causes of the fall of the blood pressure in advanced inanition it was suggested that this may possibly be associated with an expansion of the finer vessels. A general slowing of the blood flow must result which may also account for the increased frequency of the heart beat. The much increased pulse rate noticeable in advanced stages of starvation is probably a compensatory effort to overcome the falling pressure.

Upon the resumption of feeding the restoration of the marrow to the normal condition requires a long time. The bone marrow, however, quickly assumes a lymphoidal condition and cell division becomes very active. Normoblasts with one or two nuclei are present in abundance. Of course, as the inanition effect wears off cell proliferation likewise slows down considerably. The caliber of the capillary vessels in the meantime diminishes gradually again to normal dimensions.

f. Glandular Organs

1. *Liver*

Owing to the fact that this organ performs a multiplicity of functions it may naturally be expected to be more heavily taxed

than the other glandular organs. It is also possible, of course, that with the progress of the fast the hepatic cells fail to eliminate the decomposition products of metabolism. The accumulation of such waste products irritating the cells would call forth degenerative changes. The clouding and swelling which Statkewitsch observed in the very early stages is doubtless due to the disappearance of glycogen from the liver cells as soon as starvation begins which in turn affects an alteration in the colloidal state of the protoplasm. Granulation of the protoplasm and the first appearance of definite fat droplets begins when the animal has lost 10 to 15 per cent of its body weight, i.e., at the close of the first or beginning of the second inanition period. The number of fat droplets does not then increase appreciably until the second inanition period is passed (loss in weight = 20 to 25%). In still more advanced stages and usually in the vicinity of the portal vein the fat globules coalesce into drops of very large size which sometime even fill the entire cell body. Statkewitsch finds that this fatty transformation is confined to the cells of the inside of the tubule, while the outer cells have very little fat and a coarsely granular protoplasm. Meyers also noted that the cells at the periphery of the lobules was better preserved than those near the vein in the liver of a human subject who died after fifty-three days of inanition. Morgulis, Howe and Hawk examined the livers from a number of dogs which died of starvation. The histological picture presented every gradation from very slight changes to complete fatty degeneration. In one particular instance the cells have lost all normal appearance; they still retained the usual polygonal shape but the protoplasm was reduced to a mere band encircling a huge fat droplet. But even when the fatty degeneration is as complete as that, it does not extend to the entire organ and is strictly localized in distribution. Areas can be found where the cells differ from the normal only by their poorer staining quality. Vacuolization of the cell protoplasm is general and has been described by many observers.

Statkewitsch describes far reaching changes in the nuclei of liver cells, such as loss of chromatin followed by chromotolysis and vacuolization, occurring in the last stages of inanition, but in our material we found no nuclear changes of this kind.

In starving salamanders Morgulis noted pigment degeneration of the liver protoplasm, golden yellow granules accumulating

both inside and outside the liver cells. In some cases the accumulated pigment extended over a considerable area and the cells became completely filled with the granules. Usually, when the transformation of the protoplasm progressed so far and the nuclei became completely surrounded by the pigment, pycnotic changes in the nuclei occurred. In the human liver at a fatal termination of fasting Meyers also found a good deal of pigment.

2. *Salivary Glands*

The lobules of the parotid are reduced to about 0.6 to 0.8 of their normal size. The protoplasm in the very early stages of the fast shows evidence of swelling and clouding but granulation of the protoplasm and occasionally fatty transformation do not appear until the most advanced stages are reached. In the submaxillary gland Statkewitsch found fatty degeneration of the mucous cells but in Meyer's experience with human material these were even better preserved than either the crescent or albuminous cells. In the preparations which were studied by Morgulis and collaborators nothing noteworthy was discovered: the protoplasm stained faintly and was clear and homogeneous; the cells had the ordinary resting appearance with the nuclei occupying the center. Meyers found aggregations of lymphocytes around the salivary ducts.

3. *Pancreas*

In the very advanced stages of inanition the acini though greatly reduced in volume may still show good preservation, but the tissue of the islands is often hard to recognize and may even disappear.

4. *Thyroid*

Missiroli finds that almost as soon as rabbits begin to fast the colloid material ceases to be eliminated but accumulates and distends the follicles. Meyers made a similar observation in the human subject. The epithelium of the acini is very low and typical of the gland with diminished secretory activity. When the animal is again fed the colloid is very quickly discharged which fact leads Missiroli to believe that the colloid is in some way necessary in the utilization of material absorbed from the intestinal tract. "Fatty degeneration" of the colloid has also been observed occasionally in advanced fasting.

Jackson, in an extremely fine investigation of the thyroid of the rat, points out that under the influence of inanition "the epithelium of the follicle apparently undergoes at first simple atrophy which affects the cytoplasm more than the nucleus. The cells then become reduced in height, with relatively large nuclei. In advanced stages of inanition degenerative phenomena become increasingly evident. The follicular cells may remain *in situ,* but usually are desquamated replacing the colloid. The cytoplasm, typically vacuolated in the earlier stages, may become collapsed, deeply-staining and more or less homogeneous in appearance, or may disintegrate forming an irregular granular mass." The nucleus has been found to stain more deeply but this may simply be due to the fact that as the nucleus diminishes in size the chromatin mass becomes more compact. Jackson furthermore describes karyopycnotic and karyolytic changes in the nuclei. By far the most significant fact, however, is that all these inanition changes in the thyroid are characteristic to a greater or less extent for a wide range of other conditions and are identical to those recognized by pathologists in various other tissues.

5. *Parathyroids*

Pepere in both the starving dog and human subject observed atrophy of the parenchyma, with great reduction and vacuolization of the cytoplasm. The nucleus becomes hyperchromatic, i.e., it stains more deeply but otherwise the parathyroids seem relatively less affected than any of the other visceral organs. This agrees well with Jackson's description of the parathyroid glands of starving rats, except that in the advanced stages he finds also evidence of such nuclear degeneration as pycnosis and karyolysis.

6. *Thymus*

The structure and size of the thymus is affected not only by age of the animal but also by such circumstances as undernutrition or chronic and wasting disease. Friedleben noted in fasting dogs that the reduction in size of the gland was considerably greater than that of the entire body or that of any other glandular organ. Hammar found in the thymus of the fasting frogs and rabbits a loss of lymphocytes, diminution of the num-

ber of mitoses and other profound changes even to the complete disappearance of the Hassal bodies. Jonson in a careful investigation of the thymus of rabbits which have been subjected to acute and chronic starvation corroborates the fact of a rapid involution of the gland. Nine days of inanition results in a reduction of the thymus to about one-fourth of its original weight. The effect upon the parenchyma is especially pronounced, it being reduced to about ten per cent. Under chronic inanition the reduction of the gland is still more marked, to just about three to four per cent of the original weight. The cortex suffers in particular: after five days of starvation it is only about one-fifth of the normal size, and afterwards disappears almost completely. This is attributed chiefly to the degeneration and emigration of lymphocytes. However, since the mitotic activity also decreases very much the reduction must be partly due to the failure of the cells to divide. Although mitotic activity does not actually stop at any stage, nevertheless in four days of fasting the total number of mitoses in the gland diminishes from 28,-500,000 to only 6,500,000. The number of Hassal bodies likewise decreases. The unicellular bodies are apparently less resistant and diminish from 170,000 to 44,000, while the number of the multicellular bodies changes from 741,500 to 352,700.

7. *Hypophysis*

Guerrini who studied the hypophysis of the dog, rabbit and pigeon found that in advanced inanition the staining capacity gradually decreases and the protoplasm become vacuolated. Essentially the same changes were observed by Jackson in the starving rat. In the pars nervosa the only difference noted in the course of inanition is the loss of cytoplasmic granulation. The cytoplasm tends to become homogeneous and frequently also finely vacuolated. The darker staining of the nucleus is in all probability due to a condensation of the chromatic material. It is interesting to note that wherever pronounced nuclear degeneration appears, such as pycnosis, Jackson found by means of staining reactions that the acidity of the surrounding protoplasm is increased.

In the pars anterior the inanition changes are extremely variable, normal areas coexisting with others showing considerable modification. The cytoplasm is usually reduced in volume, fre-

quently much vacuolated and stains very poorly. The colloid material in the pars nervosa is apparently unaffected by the inanition.

In the starved man Meyers found that the epithelial cells were greatly reduced and degenerated, but small masses of colloid still persisted.

8. *Adrenals*

Meyers finds that the parenchyma of the adrenals of a starved man has in places completely disintegrated, and that in the medulla the cells become much vacuolated. Venulet and Dmitrowsky claim that the chromaffine substance disappears during fasting and that by the administration of adrenalin it is possible to prolong the life of the starving organism. Lucksch, however, maintains that the chromaffine tissue is not affected by starvation.

9. *Kidney*

A very interesting series of changes occurs in the kidney in the course of inanition. Here one meets with a variety of effects following a definite distribution. In the very early stage of inanition cloudy swelling and fine granulation of the protoplasm may appear as is the case also in many other tissues. But the truly degenerative phenomena occur only in the very advanced stages. At that time one may generally find thickening of Bowmann's capsule which encloses the glomerulus. Along the tubule one encounters various grades and phases of degeneration, the tubules frequently containing casts of different kinds—cellular, hyaline, granular. The cells of the convoluted part of the tubule are coarsely granular and invariably vacuolated. Occasionally in kidneys of dogs which died from starvation we observed vacuolization so extensive as to give the tubule a strikingly honey-combed appearance. At the same time the cell boundaries seem to dissolve causing a confluence of the tubular cells into a continuous syncitium. In Henle's loop, both the ascending and the descending limb, vacuolization of the cell is an extremely rare occurrence. On the contrary, according to Statkewitsch, fatty degeneration resulting in the dissolution of the individual cells with the formation of casts or cylinders is a common phenomenon in the loop. The cells of the collecting tubules as well as the straight tubules of the medulla reveal very

little change. Their protoplasmic content is homogeneous and glass-like, free from granules with a clear zone surrounding the nucleus. Here and there cells can be seen without nuclei, but when these are found they are relatively large and round, bulging out conspicuously into the lumen of the tubule.

10. *Gonads*

The sexual glands are not essential to the existence of the individual, though of prime importance for the perpetuation of the race. In the preceding chapter dealing with the influence of physiological inanition it has been amply demonstrated that the gonads may develop very rapidly under the circumstances and at the expense of other organs of the starving organism. The condition is different in experimental inanition. Heidkamp has shown that in starving fresh water salamanders (*Triton cristatus*) the fully developed eggs of the female are the first to become absorbed and utilized as nourishment by the fasting animal. Morgulis made similar observations on the newt *Diemyctylus*, namely, that the ripe female withstands inanition more effectively owing to the fact that the large reserve of nutrient material stored in the mature eggs is being gradually absorbed, thus saving the other organs and tissues from being wasted.

Grandis and Simonowitch both observed that in the testes the cells lining the seminiferous tubules which can give rise to all other cells preserve their normal character for the longest period of time. Pronounced phenomena of degeneration, such as fatty degeneration, vacuolization and even necrosis may, however, appear in the advanced stages of inanition, but even then parts of the parenchyma remain entirely normal and coexist with degenerated portions. In areas which are unaffected Simonowitch found that the seminiferous tubules in rabbits and in guinea pigs are filled with live spermatozoa; Loisel from his studies of the spermatogenesis of the starving dog concludes that the process stops. This agrees with Grandis' investigation carried out with starving pigeons in which he also showed that no new spermatozoa are produced in the course of inanition though the sperms already formed may continue to grow. Grandis found that the spermatozoa within the tubules generally die.

It is clear from these investigations that the sexual elements are subject to pronounced degenerative changes, a fact that may

perhaps account for Ugriumov's interesting discovery—discussed in a previous chapter—that young born of starved males possess distinct marks of degeneration, whereas young born by underfed females (but of normally fed males) according to Rudolski show merely that they are like the mother in a state of undernourishment.

g. Muscle Tissue

The reduction in size extends to the muscle cells. Heitz found that the fibers of the heart muscle of a normal rabbit measure 13.1 by 10.5 micra, while in the fasting rabbit they diminish to 11.1 by 7.3 micra. According to Statkewitsch the papillary muscles are affected much more than the muscle of the heart wall, though in the advanced stage the protoplasm of nearly all fibers shows a coarse granular transformation. This observation is also corroborated by Okhotin who states that the fibers lose their characteristic striation in the advanced stage of fasting. The granules are not lipoid and the transformation is therefore not thought to be fatty degeneration. The nuclei remain normal but tend to become more elongated which is probably a purely mechanical effect.

When the organism has lost about 20 per cent of its weight both the diameter and the length of the muscle fibers of the intestinal tract begin to diminish and by the time death from starvation occurs they will have lost about one-fourth of their bulk. Morgulis and collaborators found in starved dogs that the cells of the smooth muscle of the intestine appear turbid and lose their longitudinal fibrillation. The fibers become widely separated from each other, giving the muscle a very loose texture. The nuclei are irregular in outline and stain faintly with Delafield's hematoxylin.

The striated muscles are affected somewhat more quickly than the smooth muscles. Swelling is also more common and especially with the prolongation of the fast the striated muscle fibers increase owing to this phenomenon. In the last stage of inanition the cross-striations disappear almost completely. Moulton measured the diameter of fibers of the biceps muscle of steers which through underfeeding for many months lost about 45 kilograms of muscle tissue. The diameter of the fiber was reduced to 20 micra, whereas in a fed steer it usually varies from 50 to 45 micra. The length of the fiber also diminished

from 14.4 micra to 10.9 micra in steers kept at maintenance and to 6.4 micra in the underfed animals. The relative volume of an average muscle segment was 9,000 cubic micra for fat and 5,500 for thin steers, but only 640 for the starved steer. In spite of this very great reduction in size the muscle fiber showed no evidence of disintegration retaining intact its vital structure.

h. The Nervous System

From a morphological point of view the nervous system which suffers the least under the stress of inanition presents a particular interest. Certain significant alterations in the nervous responses have already been pointed out in the chapter on the physiology of inanition. It is safe to assume that at any rate during the first half of inanition no appreciable morphological effects appear. In the advanced stage, however, atrophic changes in ganglion cells and in cells of the brain and cord have been noted. Already the earliest students of this problem, Mankowski and Rosenbach, described such general effects as turbidity, pigmentation, granulation, loss of staining power as well as widely spread vacuolization. These symptoms of degeneration seem, however, to be confined to the nerve cells only and are not seen in the nerve processes or in the neuroglia. Downerowitsch noted in starved rabbits that the diameter of both nuclei and nucleoli of of the nerve cell from the cervical and lumbar spine region was reduced 14 to 17 per cent. Peri studying rabbits, cats and dogs in most advanced stages of inanition, when they have lost over 40 per cent of their weight, finds that the changes in the nervous system are primarily atrophic with only occasional evidence of hyaline degeneration. In the axis cylinder, except for the reduction of the myeline substance, no other effect was visible. Monti using the Golgi method of preparation arrived at the conclusion that the nerve cell processes assume the same varicose structure which occurs also in cerebral embolism. It is possible that in either case the change in the nerve-processes is associated with defective oxidation.

With regard to the finer structure of the neurone there is considerable discrepancy of opinion. Schaffer with the aid of Nissl's method showed that in rabbits fasting without water chromatolysis begins in the perinuclear region and is so extensive that ultimately the protoplasm appears filled with a spray of fine

granules formed by the breaking up of Nissl bodies. The nucleus ordinarily remains unstained, but under the influence of inanition begins to take up the coloring matter, the staining gradually growing so intense that the nucleolus is indistinguishable from the rest of the nucleus. Frankenberger described a similar condition of the nucleus during starvation. Contrary to Schaffer's results, however, Jakobson could detect no modification in the Nissl bodies of nerve cells from the anterior horn of the cord, neither in a hedgehog after several weeks of hibernation nor in rabbits after seven to ten days of fasting. The matter has also been investigated by Martinotti and Tirelli who employed the microphotographic method. These authors concluded that the structure of the nerve cell remains intact during inanition. The Nissl bodies lose their affinity for the coloring matter but do not actually disappear. They therefore assume that no chromatolysis or destruction of the Nissl bodies takes place, the substance simply undergoing a chemical change which affects its staining affinity. This would seem to dispose of the hypothesis which ascribes to the Nissl bodies a nutritive function in the nerve cell.

The results of Martinotti and Tirelli correspond to those obtained also by Marchand and Vurpas for the early phases of inanition. But in the very advanced stages the latter found a general breaking up of the Nissl bodies into a fine spray of granules. The vacuoles which generally appear first at the periphery soon fill up the entire cell body and the nucleus becomes invisible. The fibrillar structure of the cell is tenaciously preserved except where the fibrils are impinged upon by the vacuoles. The fact that vacuolization starts on the periphery of the cell may perhaps be due to impaired respiration there.

Reviewing the various changes which have been observed in different organs we can readily recognize certain degenerative alterations common to all, viz. vacuolization, loss of staining capacity, granulation, fatty transformation, pigmentation, and more rarely hyaline or even waxy transformation of the protoplasm. In other words, the morphological changes observable in advanced starvation are practically identical with those generally found in every pathological condition and present nothing peculiar. It may be suggested, therefore, that all pathological changes of tissues are primarily inanition effects. The rapidity with which this inanition effect becomes so great as to result in

easily discernible pathological alterations depends entirely on the nature of the inanition. It is well to emphasize that although the ultimate result of inanition is invariably the same its onset may be quicker in some forms of starvation than in others. Thus, for instance, fasting with water produces the same morphological effects as does fasting without water, but a longer time is required for the symptoms to appear, while partial fasting is slower yet in bringing on the pathological changes. Oxygen starvation (asphyxia) on the contrary produces the effect most rapidly.

Apart from the purely pathological phenomena occurring in the terminal stages of fasting, it should be mentioned that the histological peculiarities appearing at the very beginning of inanition are associated with changes in the colloidal condition of the protoplasm and are not at all degenerative in kind. The progressive atrophic changes coincident with inanition are simply due to the gradual withdrawal of metaplasmic inclusions which represent the nutritive reserves of the cells. The atrophic diminution of both cells and nuclei does not, therefore, present a pathological phenomenon either. Moreover, the morphological processes in inanition are not invariably destructive, cell proliferation going on even when the organism has been deprived of nourishment for a long time.

CHAPTER V

PARTIAL INANITION

By partial inanition we mean a condition when only one of the various substances essential for the organism's subsistence is wanting. The effect of partial deficiencies is ordinarly much more deleterious to the organism than a complete fast. The study of the problem is, however, beset with greater technical difficulty inasmuch as the total exclusion of any one particular component of the diet is frequently well nigh impossible. For this reason the experimental results obtained from studies of partial inanition are sometimes inconclusive, while the interpretation of others requires a radical revision in the light of knowledge acquired in recent years. Although the expression "diet" is commonly used with regard to such substances only as the organism receives with its food, we are employing the term in a much broader sense to include everything which the organism must get from its external environment in order to maintain its existence unimpaired for any length of time. The deprivation of the organism of one substance (for instance, oxygen) will lead quickly to a fatal termination, while that of another (for instance, carbohydrate) may have little or no immediate effect at all upon its well-being.

a. Oxygen Starvation

The problem of the relation of oxygen supply to continued existence has a broad biological significance and has aroused much interest ever since Spallanzani's discovery that the little animalcules, *Anguilla aceti,* are endowed with a most remarkable capacity of enduring lack of oxygen. This capacity, however, is not shared by many organisms, and is not a property common even to lower organisms. Thus, Loeb found that *Copepods* are exceedingly sensitive to the withdrawal of free oxygen. In a series of interesting experiments Loeb has shown that the resistance of the developing egg of different species to the lack of

oxygen varies greatly. The eggs of the fish *Ctenolabrus* are injured almost immediately when their oxygen supply is cut off, the segments of the dividing egg tending to fuse into a syncitial mass. The eggs of *Fundulus*, on the contrary, are very resistant in this respect. Even in the *Fundulus* embryo the heart may continue beating for 10 hours in the absence of oxygen, though the rate of the beat is reduced from 120 to 20 per minute. In these experiments it is not certain, of course, that the oxygen was completely eliminated, but no more than mere traces could have been present. When there is no free oxygen available the oxidation which furnishes energy for the heart beat must be carried on with the aid of intramolecular oxygen. Pflüger in his classical experiments on frogs showed that they continued to live and to eliminate carbon dioxide in an atmosphere of pure nitrogen, thus definitely demonstrating that oxidation under the circumstances must take place through molecular rearrangement. Where there is no intramolecular oxygen present or where the supply is inadequate, as in the case of *Ctenolabrus* eggs or in *Copepods*, the effect of the asphyxia makes itself felt almost immediately upon cutting off the inflow of atmospheric oxygen. Loeb, therefore, very properly concludes that the observed morphological effect (fusion of cells) results from a chemical transformation of the protoplasm.

In more highly differentiated organisms complete want of oxygen has a quick and disastrous effect, doubtless because the important centers in the nervous system easily succumb to the lack of oxygen. Asphyxia of the tissues follows within a few minutes, terminating in the death of the organism. But while complete absence of oxygen kills promptly, partial reduction of the oxygen of the air breathed by the organism—when this falls below a certain limit—produces a series of effects characteristic of oxygen starvation. Hoppe-Seyler and Araki were the first to demonstrate that a deficiency in oxygen leads to the appearance of lactic acid in the urine. Araki obtained the same results when the processes of oxidation were interfered with by various means (cooling, loss of blood, etc.). Later Reale and Boesi showed that under the conditions of oxygen insufficiency there is likewise an increased elimination of oxalic acid and acetone. These authors found that in the case of dogs respiring air poor in oxygen the protein metabolism is increased. The elimination of ammonia (doubtless associated with the large

amount of acid waste products) and that of neutral or unoxidized sulfur was likewise increased. Terray could find no change in the respiratory metabolism of a dog living in atmospheres containing oxygen in proportions varying from 10.5 to 87 per cent. When, however, the oxygen of the respired air fell below 10.5 per cent, the effect revealed itself in an exaggerated respiratory activity. With the further reduction of the oxygen content to about five per cent, lactic and oxalic acids appeared in the urine, which also contained albumin and occasionally sugar. The albuminuria is probably due to the influence of the partial asphyxia on the renal epithelium. At the same time the carbon dioxide elimination also increased while the alkalinity of the blood diminished. Asphyxia commences when the oxygen content of the air falls below three per cent, one-seventh of the normal content.

Even before Hoppe-Seyler and Araki made their interesting observations on the effect of want of oxygen on the intermediary metabolism, Albitzki investigated the influence of partial oxygen starvation on the dog. He failed to note any change until the content of oxygen in the respired air diminished below nine per cent. With the reduction of the oxygen to eight per cent the body temperature fell from 38.3° C. to 36.6° C. and continued falling even more abruptly with further reduction of the oxygen. In an atmosphere containing only 4.8 per cent oxygen the body temperature fell to 33.1° C. in seven hours, and on prolonging the experiment, dropped to as low as 28° C. With the oxygen content below eight per cent hemoglobinuria always occurred, varying in intensity directly with the lowering of the oxygen content. The red cells were actually disintegrating, the urinary tubules being frequently clogged with products of hemoglobin decomposition. As might be expected under such circumstances, the secretion of bile during oxygen starvation is also greatly increased.

These facts gain particular interest in conjunction with Henderson's theory of the asphyxial blood changes. According to this theory the lactic acid produced under oxygen want does not bring on a condition of acidosis, the symptoms, on the contrary, being those of a state of alkalosis. The former condition is characterized by a high H_2CO_3: $NaHCO_3$ ratio in the blood, while the latter is due to a low ratio between the two and, therefore, to a diminished hydrogen ion concentration. The responsiveness of the respiratory center to changes in hydrogen ion concentration varies with the oxygen tension in the blood and in such a manner

that its sensitiveness increases as the oxygen tension falls and vice versa. When the respired air contains less than 10.5 per cent of oxygen, the oxygen tension in the alveoli is likewise reduced and the responsiveness of the respiratory center is at the same time intensified. Thus the breathing, as was actually observed by Terray, becomes labored and the overventilation tends to reduce the H_2CO_3: $NaHCO_3$ ratio below normal, thus inducing a state of alkalosis in the organism. The lowered alkalinity of the blood is unquestionably due in a measure to the loss of base ($NaHCO_3$) utilized for the neutralization of lactic acid which is removed through the kidney as sodium lactate.

Complete withdrawal of the oxygen from the blood, or anoxemia brings all living processes to a stop with incredible rapidity. Anoxemia affects every organ directly, but the brain is especially sensitive to oxygen want. According to Barcroft, acute anoxemia, if it does not last long enough to push the subject too close to the brink of death, may be the cause of such far-reaching effects that in a healthy person they will persist sometime for weeks and in the unhealthy will occasion irreparable damage. Chronic anoxemia, on the other hand, encountered, for instance, at very high altitudes, incapacitates the organism for much physical exertion since the excessive work of respiration, whereby the organism compensates for the low oxygen tension in the air, consumes all available energy. The process of compensation is associated with a modification of the chemical properties of the blood, both the carbonic acid and the alkali reserves diminishing, as is also assumed by Henderson. Barcroft distinguishes three types of anoxemia or oxygen want in the blood. The first type occurs when the air does not dispense sufficient oxygen to the lungs, as in mountain sickness, the partial pressure of the oxygen in the blood naturally diminishing. This is the so-called anoxic type characterized by great unsaturation of the hemoglobin and low oxygen tension in the blood. The second, or anemic type is associated with an actual deficiency of active hemoglobin due either to a low percentage of hemoglobin, to a transformation of hemoglobin to methemoglobin, or to a preemption of the hemoglobin by carbon monoxide. The third type of anoxemia is neither caused by a deficient oxygen supply nor by a lack of active hemoglobin, but results from circulatory disturbances, the blood failing to reach the tissues and deliver a quantum of oxygen necessary for their metabolic processes. This

happens, for instance, in hemorrhage or shock. The chronic oxygen deprivation occasioned by all three types of anoxemia are somehow compensated for by the organism but the anoxic type is the most serious because its effect is the most general. In all these conditions of oxygen starvation a liberal supply of oxygen seems the only rational aid to the organism in its self-regulatory attempts.

b. Water Starvation

(*Dry Feeding*)

By far the largest component part of every living organism is the fluid portion. Apart from the water in molecular combination, the tissues are actually bathed by body fluids so that these may be truly regarded as being suspended in a liquid milieu. The tissue fluids are absolutely essential to the life of the organism, for as the ancient saying was, *corpora non agunt nisi fluida.* The existence of the organism is very rapidly imperilled when its fluid content is appreciably reduced. When an animal is subjected to complete inanition, especially where the loss of moisture through perspiration is insignificant, the decomposition of organic matter usually sets free sufficient water to satisfy the needs of an efficient circulation of body fluids. The experience with starving animals which were supplied with drinking water has generally led to the conclusion that this somewhat prolonged their resistance to inanition. In the case of humans who fasted voluntarily it was found necessary to allow a liberal amount of water in order to allay the gastric pangs and to maintain a favorable water balance in the organism and, thus, prevent unnecessary physical discomfort. But during inanition with or without water the relative water content of the body tends to increase, which is quite different from the condition in water starvation. Water is lost from the body in excessive amounts producing a true state of water starvation under various circumstances. The effect of the loss may be temporary or it may actually cause death of the organism. Excessive vaporization favored by respiring dry and warm air or by increased perspiration, or partaking of large quantities of purgatives, may all bring about a great loss of water from the body. One of the most notable cases of a serious inroad into the fluid content of the organism is represented by the extreme diarrhea of Asiatic cholera, which causes considerable condensation of the body fluids

and results in death. The tissues of cholera patients were found to contain ten per cent less water than normally. Falck and Scheffer found that the organs from dogs which died of thirst were about four per cent poorer in water than those of normal dogs.

Nothwang experimented by feeding pigeons on dry peas. He observed that the birds kept on such a dry diet displayed great restlessness accompanied by convulsions and drooping of the wings. These symptoms appear after only two days of dry feeding and can, therefore, hardly be regarded as due to an attack of polyneuritis. The pigeons died in about four and a half days, sustaining a much smaller loss in weight than starving pigeons do in the same length of time. The dry-fed (water-starved) pigeons lost hardly 10 per cent of their nitrogen store while starved pigeons generally lose about 40 per cent of their nitrogen at the time of death. Of course, the fact that death from water-starvation intervenes much sooner may account for the less extensive tissue disintegration. This leads to the conclusion that death from water-starvation, unlike that from complete inanition, cannot be due to excessive protoplasmic destruction but must be associated with some important organic disturbance. Indeed, profound changes in the chemical composition of the tissues are known to occur. The ash content of the muscle substance increases somewhat under the influence of the dry régime. Especially noteworthy is the increase in the quantity of extractives. The total quantity of extractives in the pigeon increased from 15.9 to 17.2 per cent of the dry material. Besides, the extractives from the water-starved pigeons are decidedly richer in sodium chloride, phosphorus and nitrogen than the extractives from normal pigeons. The P_2O_5 content rises from 1.028 to 1.158, and that of the nitrogen from 9.21 to 11.6 per one hundred part of extractives. But the greatest change occurs in the water content of the organism. This is shown in a most striking manner by Nothwang's comparison of normal, fasting and water-starved pigeons. On a fat-free basis there was 76.96 per cent of water in the muscles of normal birds and 73.04 in the rest of the body including bones, but in the pigeons kept on dry food the muscles contained only 70.63 per cent and all the other organs combined 66.08 of water, proving unmistakably a desiccation of the tissues. In the pigeons subjected to complete inanition, on the contrary, there was a relative enrichment of the tissues with water, the

percentage in the muscles rising to 81.64 per cent and that of the remaining organs to 74.57.

The study of the influence of water starvation is often unsatisfactory owing to the fact that the animals deprived of water generally lose their appetite and refuse to take the dry food or vomit what they may have eaten. This, of course, greatly complicates the matter, as the animal, for part of the time at any rate, is under complete starvation. Landauer attempted to minimize this complication by gradually reducing the quantity of water given to the dogs experimented on. He found that the partial water-starvation caused an increased protein metabolism as may be judged by the greater elimination of nitrogen, phosphorus and sulfur in the urine. These findings are also corroborated by Dennig who noted that thirst may raise the nitrogen excretion 29 per cent; owing to the poor absorption in the first day the nitrogen elimination may show a transitory decrease, but the continued abstention from water finally leads to an increased nitrogen excretion. Straub, who fed dogs on dry meat powder mixed with melted pig fat, essentially substantiates the work of Landauer. He found the blood of his dogs to have been impoverished in water to the extent of 2.5 per cent, and this condensation may possibly account for the fact that during the dry feeding the pulse pressure diminishes greatly (from 50 to 15 mm. Hg) while the mean blood pressure remains unchanged. Apparently most of the force of the heart is used up in overcoming the greater resistance caused by the increased viscosity resulting from condensation.

Both Straub and Spiegler consider the increased nitrogen elimination as due to excessive protein katabolism and not to a mere flushing out of the tissues, inasmuch as the quantity of urine voided on normal and thirst days is not materially different. The enhanced protein katabolism bears a certain resemblance to the condition in infectious diseases where the protein substance is wasted very much. In fevers this wasting of the tissues may be counteracted by a free supply of carbohydrates, which excel in the ability of sparing the proteins from katabolism. The results with dry feeding offer also a *raison d'être* for the free use of the water therapy, especially in conjunction with glucose, as a particularly potent means of checking waste of the valuable protein moiety of the protoplasm.

The close relation between water starvation and infectious

fever is further exemplified by the researches of Pernice and Scagliosi, who experimented with dogs and chickens. The latter thrive for a long time on dry food and experiments with them are, therefore, less vitiated by the intervention of complete starvation. The dogs, on the contrary, eat very little of the dry food and as the experiment goes on stop taking the food altogether. A study of the cellular composition of the blood and of the hemoglobin demonstrates beyond doubt a gradual progressive desiccation, or condensation of the blood. The number of red cells in the dog gradually increases from 5.2 to 7.4 million; the percentage of hemoglobin also increases from 65 to 105 in six days, while the color index remains practically unaffected. The cell count and the hemoglobin again diminish as the animals consume less and less of the dry food, but in the last few days preceding death, when the dogs take no food at all, the blood count and the hemoglobin content return to the original normal level. The animals died before they had lost 25 per cent of their body weight. It would have been interesting and most valuable from a theoretical standpoint to determine whether the administration of water at this critical stage would restore to the animal its former resistance. The chickens continued to eat the dry food and in large enough quantity almost to the very end of the experiment. It is to be noted that the condensation of their blood—as can be judged from the uninterrupted rise in the number of red cells and of the percentage of hemoglobin—also continued to the very end.

The number of white cells shows two distinct changes: at first, there is a sharp diminution in the number as has generally been observed in various inanition states. In all probability, this leucopenia is associated with the same phenomenon of migration already discussed in connection with hibernation and acute experimental inanition. This supposition is borne out by Pernice and Scagliosi's observation that the interstitial tissue of the elementary tract, kidney, etc., is filled with immigrated leucocytes. Under the conditions of dry feeding, however, the depletion of the blood of its white cells is only temporary and is followed by a leucocytosis which develops to a striking degree. Thus in the dog the number of leucocytes, having diminished to 9,300 on the fourth day of dry feeding, commences to rise again reaching ultimately the high level of 41,850 per cmm. just a few days before death. A similar leucocytosis was observed also in the

chickens, and this suggests that the water-starvation is undoubtedly associated with a febrile condition akin to an infectious attack.

Although both the dogs and the chickens consumed dry food during the larger part of the experiment, their emaciation had been general. The post-mortem examination shows that the muscles are pale and dry, their capsules being all wrinkled. The pericardial sac is almost devoid of fluid. The brain, spinal cord, kidneys, stomach and liver are hyperemic owing to much congestion. Microscopically, too, the cells of the nervous system reveal poor staining capacity, especially in the anterior horn of the cord, where many atrophic cells are to be seen. The condition of the muscles is similar to that found in advanced stages of inanition: the cross-striations are not conspicuous, the fibrillæ are very thin and, therefore, appear widely separated. Furthermore, a multiplication of the nuclei is often observed, as has also been described in the muscle fibres of animals which succumbed to complete inanition. The intima of the blood vessels presents unmistakable signs of inflammatory processes which may even extend to the heart. The cells from many different organs show atrophy and are smaller and stain poorer than normal cells. Vacuolization, especially of the epithelial cells of the alimentary canal as well as of the cells of the central nervous system, is very extensive. The glands in the pylorus region are infiltrated with leucocytes, which in places are so numerous as to look like incipient lymph nodules. To complete the picture of the morphological alterations of the tissues from animals subjected to water-starvation it should be mentioned that alongside of atrophic and degenerative changes one also finds cells in the process of mitotic division. Of course, inasmuch as the animals deprived of water finally refuse to take their food, and, therefore, die in a state of total inanition, it is not easy to say whether the observed changes are entirely due to the water-starvation or to the general inanition. It is, however, noteworthy that the morphological changes are essentially the same as in the advanced stage of acute and complete inanition, but are apparently brought on more quickly than under that condition.

The subject of the water-starvation should not be dismissed without indicating the bearing of these experimental data on the therapeutic application of a dry dietary, generally known as the Schroth treatment. This dietetic regimen is based upon a drastic

restriction of the intake of fluids. It was originated by a peasant, Schroth, and later found a devotee in the famous physician, Cantani, who elevated the diet to a scientific system. Cantani employed his dietetic procedure of feeding patients with stale rolls in a variety of affections such as gout, rheumatism, diabetes, etc. Of course, it is extremely doubtful that Cantani's success was the result of improvement in the tissue oxidation induced by the dry diet. A diet of dry rolls is deficient in every nutritive constituent and patients on the Schroth diet are to all intents and purposes starving. The diet unquestionably favors tissue decomposition as the increased nitrogen excretion indicates, but it remains to be shown that this is not the outcome of the fever which generally accompanies dry feeding. As a means of reducing obesity, however, the value of the Schroth cure may be definitely questioned. Nothwang's dogs on a thoroughly dry diet suffered little loss of fat, while other dogs, subjected to complete fasting for a similar period of time, lost a considerable portion of their fat content. In a sense the Schroth dry roll cure is not strictly speaking a water-starvation cure, and it seems highly probable that ordinary fasting would accomplish similar results more quickly and, what is even more important from the point of view of the patient, with considerably less suffering which the rigors of the dry diet inflict.

c. Mineral Starvation

Under the baneful influence of the theory of dietetics which dominated our ideas on nutrition for several decades and which centered attention primarily on the energy content of the food, the mineral constituents of the diet received scant consideration. Not being energy yielders in the sense our organic food stuffs are, the mineral moiety of our daily consumption has been relegated to a position of unimportance. Only within the last few years has the matter been gaining predominance in the mind of students of nutrition that inorganic substances, which do not furnish energy in the form of heat, like the fats, carbohydrates and proteins do, are nevertheless absolutely indispensable to the well-being of the organism, to its existence, growth, and reproduction. Salts of various kinds form invariably part of the protoplasm, and in certain tissues, like bone, actually constitute the major portion. The permeability of the cell membrane, upon

which the exchange of material with the surrounding medium depends, is modified by certain ions, while the osmotic tension of the cells and of the tissues, which is essential for the discharge of their physiological functions, rests chiefly on the presence of mineral substances. Osmotic tension contributes an internal force of such magnitude that it cannot be neglected. Furthermore, some elements, like iron or iodine, though found only in minute quantities, play an extremely important rôle as catalyzers for many chemical processes, such as carrying oxygen, while others are necessary for enzymatic activity, especially that of digestion, or in detoxicating waste products of cellular metabolism and thus preventing chronic protoplasmic poisoning. And last, though by no means the least, is the important function performed by the mineral constituents in regulating the reaction of the blood and of the body fluids. The buffer action of substances like the bicarbonates and phosphates eliminating all danger that may result from sudden and abrupt changes in the hydrogen ion concentration is too well known to require much discussion.

This enumeration of the various functions performed by the mineral components would fail to convey the full measure of their importance in the economy of the organism were no mention made of the significant fact that the inorganic elements must be present in definite proportions to secure for the organism physiologically proper conditions of existence. Certain ions, unless counteracted by others, will exert a toxic effect, and, as Loeb has elucidated in a series of brilliant researches, the salt solutions must be "balanced" in a definite way to serve the purpose of maintaining the existence of the organism. The salt content of the body fluids, lymph and blood must not merely suffice to keep up the osmotic pressure but their composition must be qualitatively adjusted in order that the muscles, the nerves, the heart may function properly. Besides, certain elements, like calcium and phosphorus, which partake in the building up of the supporting structures of the organism, must be supplied in sufficient amount to prevent the defective growth of the skeleton.

The lack of common salt in the food of itself has no ill effects either on the general metabolism or on the digestive function, as was shown by the experiments of Belli and those of Goodall and Joslin. According to Belli, however, when there is no salt added to the food the N-metabolism is increased. Under this

condition the excess of sodium chloride will be eliminated from the organism, but that part which is intimately combined is retained. This is still more strikingly demonstrated in the experiments of Grünwald, who kept rabbits on a diet practically free from chlorides. The elimination of chloride in the urine ceased almost at once, but no ill effect had been observed otherwise. When, however, diuretin was administered after the excretion of chloride stopped as much as one gram of chloride was caused to be eliminated, and if the dosage was repeated several times symptoms of toxemia appeared such as extreme muscular weakness, trembling, paralysis of hind limbs which soon also extended to the anterior portion of the body and which, in a few days, resulted in death. The chlorine content of the blood actually diminished 50 and in some extreme cases even 75 per cent. This effect was produced entirely through the withdrawal of chlorine from the tissues and not by the diuretin itself, since this had no effect whatever when administered in conjunction with sodium chloride.

It must be understood, however, that the sodium chloride may be dispensed with provided the intake of potassium salts is not excessive. Animals which subsist on a vegetable food or vegetarians whose diet is unusually rich in potassium salts show a strong craving for the salts of sodium. This, according to Bunge, is produced by an actual removal of the sodium from the tissues and, if not corrected by an adequate supply of this element in the diet, leads to an impoverishment of the tissues and body fluids creating serious distress to the organism. It is a well familiar fact that animals naturally timid and shy readily overcome their sense of fear when it concerns this satisfaction of their overpowering craving for salt. Hunters of deer, for instance, have always exploited this instinct, waiting for their game near the salt licks.

It is entirely different when the intake of all mineral matter is cut off or, at any rate, reduced to the vanishing point. Experiments which Taylor performed upon himself are very interesting because they demonstrate what effects a diet sufficient in calories but sadly deficient in minerals will produce. At first, as soon as he commenced his mineral-free diet, he was affected by diuresis which, however, passed away after two days. The secretion of water through the skin was likewise much enhanced and the diaphoresis persisted through the entire experiment. Apparently

this excessive perspiration was in some way due to a general lowering of vascular tone, the continuous sensation of warmth all over the skin indicating that the peripheral vessels were dilated. Early in the experiment Taylor lost his appetite, and after he had been for five days under the condition of rigorous exclusion of mineral substances his muscles, too, became numb and very sensitive to touch, and easily fatigued. It is possible that the constipation which he complained of was likewise to be attributed to the loss of tone of the intestinal musculature.

The older experiments of Foster, Lunin and others who attempted to solve the question of the influence of mineral-starvation are deprived of much of their significance by the extension of knowledge of dietetics which has taken place in the last several years. Foster, for instance, prepared ash-free diets by repeatedly extracting the food with boiling water. By this procedure, however, he removed many other things the existence of which was not even suspected in his day and which only within recent years we learned to associate with the prevention of such a disease as beriberi. Indeed, the pigeons which Foster kept on his "ash-free" diet show unmistakably that they have been suffering chiefly from a deficiency of the so-called water-soluble vitamin, of which more will be said in a further section. After about ten days on such extracted food, the pigeons became subject to convulsive fits, and the limbs became too weak to support the body. All these are now well recognized as typical symptoms comprising the syndrome of polyneuritis. The dogs likewise fared very poorly on the ash-free régime. The animals were rapidly affected by a general weakness and lassitude which are seldom, if indeed ever, observed in dogs even in the most advanced stages of inanition.

Lunin undertook his study at Bunge's suggestion with the view of testing the hypothesis that Foster's dogs suffered not on account of the lack of mineral matter but because of the inability of the organism to neutralize the sulfuric acid formed in the decomposition of protein. The experiments are at best inconclusive. Using a diet of more or less purified ingredients, Lunin found that on the addition of a salt mixture similar to that which is present in milk, the diet could not be made adequate for mice, but when instead an equivalent amount of milk was added the mice not only remained alive but increased in weight. Lunin's interpretation of these experiments, that the organism

requires not merely a certain quantity of mineral constituents but that these must be in organic combination (milk, not just milk salts) is, of course, erroneous. The basic diet which he employed, consisting of purified ingredients, was wanting in vitamins so abundantly present in milk. Therefore, no growth could be secured, nor indeed could the animal's existence be long maintained on this diet except when raw milk was added to it. The experiments furnish no evidence whatsoever of a need of minerals in organic combination. This problem in nutrition has been definitely settled by the experience of agricultural stations, where cattle have been raised successfully and maintained in excellent health with the mineral requirement supplied exclusively in the form of inorganic compounds.

Considerable advance has been made in the study of this problem by the refinement of the experimental methods, whereby the individual mineral constituents rather than total ash could be modified in a diet which was adequate in every other respect. Using a synthetic food mixture containing the two essential vitamin factors, Osborne and Mendel achieved great progress in analyzing the problem of the effect of mineral deficiencies. These investigators employed a basic ration consisting of 18 per cent protein, 1.5 to 2 of dry brewer's yeast, 25.5 to 27.5 of starch, 18 of butter fat, 7 of lard, and 28 to 29.5 of a lactose-salt mixture by means of which each inorganic element could be varied.

The latter mixture was prepared by evaporating 246 grams of lactose with the following quantities of inorganic materials:

$CaCO_3$	13.48 gm.	H_3PO_4	10.32 gm.	Ferric citrate	0.634 gm.
$MgCO_3$	2.42 "	HCl	5.34 "	KI	0.002 "
Na_2CO_3	3.42 "	H_2SO_4	0.92 "	$MnSO_4$	0.0079 "
K_2CO_3	14.13 "	Citric acid	11.11 "	$K_2Al_2(SO_4)_4$	.0.00245 "

By leaving out one or another of these various minerals a variety of experimental diets was prepared which served to study the influence of the absence of a particular element. It should be noted, however, that even with this experimental technic it was impossible to procure diets that were really free from the particular substance in question. On rations wanting either magnesium, sodium or chlorine the rats grew vigorously. As there was present less than 0.04 per cent of either sodium or chlorine, it is evident that even such traces are sufficient to secure com-

plete growth. Good growth was also obtained with as little as 0.01 per cent magnesium or with 0.03 per cent potassium. When, however, both the sodium and potassium were lacking growth ceased and could only be induced again by supplying one or the other. A lack of calcium or of phosphorus brought promptly a cessation or, at any rate, a restriction of growth. Magnesium could not replace the calcium. The very interesting results of these experiments shows that a further extension of this fruitful work is most desirable.

The important relation of the calcium and phosphorus to the growth of the skeleton has naturally attracted wide attention. Dibbelt, experimenting on pregnant dogs with diets very poor in calcium, observed that the skeleton of the new born had a perfectly normal calcium content but the mother invariably suffered from osteomalacia. Evidently, the more vigorously growing fetus not only used whatever calcium there was in the circulation, but actually caused a withdrawal of calcium from the mother's bones to furnish material for the building up of the embryonic skeleton. As much as 30 per cent of the calcium was thus drawn away from the mother's bones, which goes to show how urgent it is to furnish the pregnant organism with a plentiful supply of calcium. Aron and Sebauer found that the effect of a calcium-poor diet on the growing organism is to produce bones with a higher percentage of water than in the normal. Besides, the organic matrix remains imperfectly calcified. Heubner, Lipschütz, as well as Hart, McCollum and Fuller, experimenting with phosphorus-poor foods found that, although growth was not stopped, the young remained undersized and with markedly defective skeletons. Hart, McCollum and Fuller's pigs raised on phosphorus-poor diets had such weak bones that they were unable to uphold their bodies and would be lying down most of the time. In Lipschütz's dogs the bones remained soft and, at any rate, the fore limbs were bow shaped owing to defective calcification. Histologically, too, the bones of animals fed inadequate amounts of phosphorus revealed decided differences from normal bones, as Schmorl has shown.

Anorexia, or loss of appetite, has always been noted in animals on mineral poor diets and this, of course, must cause emaciation. Vomiting, which is likewise a frequent occurrence, would tend to exacerbate this condition. Whether this is the direct result of mineral deficiency or is occasioned by a simultaneously occurring

vitamin deficiency must at present remain an open question. Likewise, the older experiments failed to solve the problem of the importance of the minerals in the diet. There is no gainsaying that minerals like calcium and phosphorus which are indispensable building material, and others which are essential in the economy of the organism must be furnished in effective quantities to prevent the appearance of definite signs of partial starvation. But the question of mineral metabolism needs to be reëxamined in the light of our newer knowledge of dietetics and the importance of inorganic substances for growth, development and reproduction must be established by careful experimentation along the lines already mapped out by recent research.

d. Carbohydrate, Protein and Fat-Starvation

We have seen so far the consequences of restricting the intake of oxygen, water or mineral substance. None of these, of course, furnish the organism with energy. But the business of living is conducted on a basis of strict accounting. A certain amount of energy is required daily to carry on the multifarious physiological tasks, and this must be supplied adequately with the daily diet. Failing in this, the organism must needs fall back on its own reserves of energy. It will draw from the stocks accumulated in the tissues. The energy yielding foods are the chief organic components of the diet: carbohydrates, fats and proteins. It is possible, of course, to supply the organism the necessary quantity of calories and thus insure for its functional activity an adequate energy income while one or another of these food stuffs is missing either completely or partially. A restriction of the carbohydrate, fat or protein intake creates a condition which manifests itself primarily as a maladjustment of metabolism. Thus, the elimination, or even rigorous restriction of the carbohydrate component of the diet generally calls forth a characteristic reaction on the part of the organism in the development of ketosis. True, this reaction is not of universal occurrence. In man this may be provoked with relative ease even by mere restriction of the carbohydrate moiety; in other animals, on the contrary, such dietary restriction does not suffice unless the animal is phloridzinized at the same time, by which means, of course, the carbohydrate stock of the tissues is very rapidly depleted.

From results obtained in experiments extending over a limited period of time it is evident that the effect may be entirely negligible, or may manifest itself in the development of ketosis, i.e., production of acetone bodies resulting from the defective fat metabolism. Under the pathological conditions existing in diabetes, or in protracted inanition, when the organism's supply of carbohydrate has been almost completely exhausted, ketonuria is also an invariable accompaniment.

Proteins owe their importance to the fact that they not only furnish the organism with energy but that they are also tissue builders *par excellence*. The growing organism must, therefore, obtain a liberal allowance of protein in its diet in order to provide material for repairing the usual wear and tear, but especially for new tissue growth. A positive nitrogen balance during growth is an indispensable requirement. In the adult organism, however, there is an equilibrium between the amount of nitrogen consumed in the form of protein and the nitrogen which appears as the waste products of excretion. It is furthermore a significant fact that nitrogen equilibrium or balance in the adult may be established at very different levels of consumption. The existence of the nitrogen balance is sufficient guarantee that no nitrogen is lost by the organism from its own tissues. It also signifies that every excess of nitrogenous food over and beyond a certain limit goes simply to waste. It increases the functional load of the kidneys, which are principally concerned with the removal of protein waste products, without serving any apparent good purpose to the organism. These considerations formed the foundation of various dietary theories advocating a low protein régime as essential to the continued well-being of the organism. According to the orthodox view 16 to 20 grams of protein nitrogen should be supplied daily, but since Chittenden's monumental investigation it has been conclusively demonstrated that nitrogen as well as physiological equilibrium (stationary body weight) can be maintained on diets containing very much less nitrogen, with the result that the physical efficiency and the general health condition is likewise improved. The results of experiments with large groups of men in various walks of life led Chittenden to conclude that with sufficient non-nitrogenous material to supply the energy need, the daily protein requirement of an adult is only 0.85 grams of nitrogen per kilogram of body weight, or about one-half the amount called for by the conven-

tional dietary standards of Voit and Atwater. Although these conclusions have been adversely criticized, it is nevertheless well recognized now that moderation in nitrogenous food conduces greatly to the organism's welfare. Recently, Sherman reëxamined this question of the protein minimum and concluded that 35 to 45 grams is ample for a person weighing 70 kilograms. This, of course, is even considerably lower than Chittenden had assumed.

When, however, the protein is reduced below the minimum level necessary to maintain the nitrogen balance, a condition of actual protein-starvation is produced. Kinberg, who performed such experiments upon himself, consumed a diet sufficient in calories but very poor in nitrogen—only one to two grams per day—equivalent to about 12.5 grams of protein. This was about one-sixth of the minimum requirement established by Chittenden. Kinberg remained on this protein-poor diet for two weeks during which time his weight diminished from 81.5 to 79.5 kilograms. This is, of course, a much smaller loss than would have been occasioned by a complete fast of the same duration (about 10 kg.). The fact, nevertheless, is worth noting that, in spite of a liberal provision of 40 Calories per kilogram of body weight, the diet was entirely inadequate to maintain physiological equilibrium, that is, constant weight, and there was throughout the experiment a negative nitrogen balance. An examination of the daily nitrogen excretion fails to reveal the condition commonly observed in cases of complete inanition, namely, that the nitrogen elimination on the second, third, or fourth day of fasting attains a maximum value. This, as was shown in the foregoing, is associated with the disappearance of the glycogen store from the fasting organism. On the contrary, Kinberg's nitrogen elimination diminished regularly from day to day during the first week of the experiment. It then remained practically constant. The nitrogen elimination during the second week was only about 0.07 to 0.08 grams per kilogram of body weight. Levanzin even on the thirty-first day of fasting excreted 0.147 grams of nitrogen per kilogram. The very low nitrogen loss in the case of Kinberg is, of course, due to the sparing action of the carbohydrates and fats in his diet.

The nitrogen partition in the urine, during the 14 days of the protein restriction below the physiological minimum, reveals some differences from the condition as it exists in complete inani-

tion. The urea nitrogen at first diminished, and from 79.1 per cent it decreased to 68.4 on the tenth day of the experiment. It then commenced to rise once more, reaching on the fourteenth day the normal level (80.6%). In experiments with fasting men the rise in the percentage of urea nitrogen is not generally seen because of the relative brevity of those experiments. In the dog, when the fast has been protracted, it has been found that following a preliminary fall the urea nitrogen excretion rises again. The results based on partial nitrogenous fasting corroborate the findings in the case of animal experimentation.

The elimination of ammonia nitrogen shows also a distinct deviation from the condition prevailing in complete inanition. In the fasting man, as was shown previously, the ammonia nitrogen in the urine increases threefold after a few days of inanition, and continues increasing with the progress of the fast. This has been shown to be closely associated with changes in glycogen content of the body and the abnormal production of fatty acids in the absence of carbohydrate. In Kinberg's experiment the percentage of ammonia nitrogen (about 4.5%) actually diminishes in the first week and only towards the close of the second week does it rise to 7.5 per cent. These facts are fully in accord with the interpretation of the changes in ammonia nitrogen during fasting. In this experiment, with an adequate supply of carbohydrate available, there is, of course, no depletion of the glycogen stock and, therefore, no acidosis develops which requires an excess of ammonia for purposes of neutralization.

The total creatinine excretion shows also a remarkable behavior. In Levanzin's case or that of Kozawa, both of whom abstained completely from food for 31 and 14 days respectively, the creatinine nitrogen in the urine was greater than normal but showed practically no changes during the entire experimental period. Under the conditions of partial starvation, however, when only the protein moiety of the diet was deficient, the total creatinine nitrogen rose continually so that from 3 per cent in the preliminary period it reaches 9.5 on the twelfth day of protein starvation.

The failure of the organism to utilize carbohydrates under pathological conditions, like diabetes, or the lack of carbohydrates in the diet, as in partial or complete inanition, invariably lead to the development of ketonuria. The lack of sufficient

protein to meet the needs of nitrogenous repair, even when the energy requirement of the body is amply provided for by fats and carbohydrates, produces progressive wasting of the tissues. The effect which the elimination or rigorous restriction of the fat moiety of the diet exerts even on the fully grown adult organism has not yet been satisfactorily defined experimentally. This problem is particularly difficult to study because of the circumstance that fats and especially the heterogeneous group of closely related lipoids are universally distributed. It is, therefore, an extremely perplexing task to free natural food stuffs from these substances, and the problem of maintenance on synthetic food made of chemically pure ingredients has not as yet been successfully solved. The matter is still further complicated by the fact that associated with the fats there are substances of unknown constitution which are vitally important to the organism. As the next section is devoted to a consideration of these unknown substances, it will suffice to state at this moment that it is often impossible to determine whether an observed effect is due to the want of fats as such or to the absence of those admixtures which frequently go with them.

Stepp approached the problem of the indispensability of fats in the diet with the view to determining whether or not animals possess in common with plants the ability to synthesize their lipoids. When he attempted to feed mice with an adequate food which, however, was previously extracted with ether and alcohol, Stepp discovered that the experimental animals invariably died after a few weeks. The untimely death could be prevented only by adding to the food the alcohol-ether extract. Stepp convinced himself that the improvement in the condition of his mice was due neither to the presence of inorganic matter in the extract nor to the presence of neutral fats. He was unable even to postpone the death of the mice by the addition of tripalmitin, tristearin or triolein. The fact that he failed to rescue his mice fed on an ether-alcohol extracted diet when butter was added to their rations would bear reinvestigation. Apart from the alcohol-ether extract of the food, he found that milk and egg-yolk possessed potent remedial power. Notwithstanding the fact that the results of these experiments with lipoid-free diets were clear-cut and unequivocal, Stepp was cautious not to draw the conclusion that they proved the indispensability of lipoids for the

animal's existence, recognizing the alternative possibility that in the process of extraction some unknown material absorbed by the lipoid has been removed.

Osborne and Mendel were apparently successful in raising white rats to maturity (they failed to do so with mice) on artificial diets which they considered fat-free, but not lipoid-free because the foods were extracted with ether alone. Their experimental diet contained casein or edestin as the source of protein, sucrose and starch as the source of carbohydrate, while the mineral matter was supplied by a salt mixture similar in qualitative and quantitative composition to the ash of milk ("artificial protein-free milk"). The rats grew well on this diet, and Osborne and Mendel concluded that growth may take place without true fats. The failure of the rats, however, to attain full size and the fact that some of the experimental animals ultimately began to decline in weight and even died prematurely caused them to make certain reservations with regard to this conclusion. Unfortunately the authors have left a number of important points unelucidated, and it even seems doubtful that their diet was fat-free. At any rate, Taylor and Nelson [1] have shown recently that fat is held in starch in very intimate combination and can not be removed by simple ether extraction. Furthermore, the casein, too, may hold some fat which ordinary ether extraction fails to remove completely. It would seem, therefore, that the diet employed was at best fat-poor but not fat-free.

Jansen could not secure growth in rats on fat-free rations, and he was equally unsuccessful when he supplied to the basic diet such vegetable fats like cocoanut oil or olive oil. The latter are well known to be free from those vitamins, the nature and function of which we will discuss more fully in the next section, and it seems very probable, therefore, that, as Osborne and Mendel have assumed, fats *per se* are not indispensable for growth. To be sure, when Osborne and Mendel performed their experiments with the fat-free rations the nutritive significance of the vitamins was not yet appreciated. In their later work Osborne and Mendel employed adequate synthetic diets made from fat-free ingredients to which the so-called fat-soluble vitamin A was added in the form of a preparation made by concentrating the ether extract from plant leaves rich in this vitamin, or by

[1] *J. Am. Chem. Soc.*, 42, 1726, 1920.

supplying dry alfalfa leaves in appropriate quantity. The animals quadrupled their weight in the usual length of time. According to the authors the daily ration contained no more than about 0.08 grams of ether soluble matter. It is noteworthy that on these exceedingly fat-poor diets the growth of the rats proceeded, at any rate in the early weeks, at a greater rate than normally. Osborne and Mendel conclude that, if true fats are essential for growth, the necessary minimum must be very small, indeed. A careful consideration of the data fails, however, to justify fully this conclusion. If one assumes that the average body weight of the rats during the experimental period was 200 grams, it follows that the animals were getting 0.4 grams per kilogram of weight. This, of course, corresponds to 28 grams daily for an adult human being of 70 kilograms weight. When the matter is looked at from this angle, the amount of the ether-soluble matter in the rats' diet no longer seems negligible. Voit's nutritional standard calls only for 56 grams per day, and, as will be shown presently, the validity of this standard has also been seriously questioned by students of dietetics.

Many years ago Herter studied the influence of fat-starvation on growing pigs, though his work has been generally overlooked. He undertook his study with the view in mind to determine experimentally whether or not fat-starvation is responsible for the development of rickets in children. He fed young pigs for nearly a year on centrifugalized Walker-Gordon milk. This process makes the milk almost fat-free, the fat content being only 0.05 per cent, or about 0.005 of the normal fat content of sow's milk. It must be mentioned that centrifugalization does not remove completely the fat-soluble vitamin, which is rather a fortunate circumstance in these experiments. The pigs obtained no more than 0.7 grams of fat per day during the greater part of the year, and even in the last four or five weeks of the experiment, when the daily milk ration has been greatly increased, they did not get more than two grams a day. This, of course, is a much smaller relative amount than the rats in Osborne and Mendel's experiments received (about 0.05 grams of fat per kilogram instead of 0.4 grams). The pigs gained weight slowly. Certain abnormalities began to appear in the pigs after they have been on this fat-poor diet for four months. It was noted that the skin was very dry and the growth of hair scanty. These effects became more marked as time went on. Then the limbs became

weak and ultimately the pigs were entirely unable to stand. The muscles, too, were decidedly flabby though not atrophic, the hemoglobin content of the blood was very low (65%), while hemorrhagic eruptions developed in different parts of the body. Herter recognized these to be scorbutic in character.

The most notable metabolic disturbance was the abnormally high urea excretion which went parallel with the very low phosphate elimination. The latter was evidently caused by faulty absorption from the intestine, and this in turn was due to the fat-poor diet. The poor absorption has been demonstrated by an examination of the ash content of the dry feces. Normally the pig's feces contained about 17 per cent of ash, but on the centrifugalized milk diet this increased to 50 and even 70 per cent. The relation of the poor absorbability of phosphorus to the low fat content of the food has also been directly corroborated by adding suet to the food. Under this condition a reversal has been immediately effected, the urea excretion diminishing and that of the phosphorus rising markedly.

The weakness of the extremities would, therefore, seem to originate from the same cause as in the case of the pigs which Hart, McCollum and Fuller raised on phosphorus-poor diets. The percentage composition of the femur, as far as calcium phosphate or total ash is concerned, remained unchanged, but the development of the skeleton was greatly retarded. In either case we are dealing with an effect of phosphorus starvation; in one instance, the condition is brought on by poor absorption due to a lack of fat; in the other, by an actual insufficiency in the supply of phosphorus. It is most probable, therefore, that the weakness of the limbs observed by Herter was not really the result of rickets but was due to an underdevelopment of the bones caused by partial mineral starvation and by scurvy.

The histological picture also studied by Herter offers many interesting points. The fatty tissues in fat-starvation undergo gelatinous atrophy as is also the case when animals are subjected to total inanition. "The most obvious consequence of fat-starvation is a universal serous or gelatinous change in the subcutaneous and other fat depositories. After a few months of fat-starvation the fat cells shrink somewhat, but their contents continue to consist wholly of fat. Next, the contents of some cells break up into larger and smaller fat globules and a material between these globules which is not fat and stains feebly

with hematoxylin and basic aniline dyes. This change becomes universal; the cells diminish very much in size and the cell membrane grows irregular owing to a diminution in volume of the cell body. The nucleus is no longer applied to the cell membrane but may occupy any position in the cell. In the course of time, the much shrunken contents of the cells contains no fat and consists merely of a small amount of homogeneous material, staining faintly with hematoxylin, and occasionally fine granular matter near the nucleus."

Herter's experiments, though seemingly demonstrating the deleterious effect of fat-starvation, may really be interpreted in an entirely different sense. It is clear that the bone defects were only secondary to the absence of sufficient fat; the changes in skin and hair growth as well as the scorbutic eruptions must have been associated partly with a deficiency of the centrifugalized milk in the essential vitamins and partly with a lack of variation in the diet. The low hemoglobin content of the blood is easily to be accounted for since milk is a notoriously poor source of iron and an exclusive milk diet is always responsible for anemia. A certain amount of vegetable matter added to the milk diet would, no doubt, have corrected these untoward effects. As for the effects of the lack of fat itself, the results, therefore, seem to narrow down to morphological changes in the adipose tissues. It is very probable that a more liberal allowance of carbohydrates might have caused some relief, too. At any rate, in one experiment a pig was given an excess of carbohydrates, and this one suffered much less than the other animals. It is possible that a synthesis of fat from carbohydrate was effected. If one recalls that the pigs obtained only one two-hundredth part of the fat found in the food of normally nourished pigs, the question is not amiss: Would it be possible to raise pigs in good health and assure them a normal rate of growth with a fat allowance only one-hundredth, or one-fiftieth, or perhaps one-tenth as large as that which nature provides in the sow's milk? From all we know this does not appear outside the range of possibility.

So far the problem of fat-starvation has been considered in its relation to the effect on the young growing organism. In the next section this subject will be discussed further, but the way has already been cleared for answering the question as to the influence of a restricted fat intake on the fully grown adult organism. The problem is important sociologically in the same

degree as the question of the protein minimum, and both deserve careful consideration in social economy. The truth of this statement has been fully demonstrated by the events of the World War. Orthodox dietetics prescribes, together with a high protein intake, at least 56 grams of fat per day. Scientific opinion with regard to the former dictum has swerved, however, more in the direction of moderation but voices are also being lifted against the fat requirements of our dietary standards. Schittenhelm and Schlecht hold the fat shortage responsible for the incidence of the war edemas. This view, however, does not seem tenable since Kohman has demonstrated experimentally that edema is in no manner associated either with the lack of fat or with vitamin deficiency but is due to a general undernutrition produced by a low protein diet of low caloric value.

The cause of low fat diet has been championed by Hindhede, the veteran student of dietetics. He conducted feeding experiments with healthy young men, extending over a period of a year and a half, and still being continued. These men have been living on a diet consisting exclusively of bread, potatoes, cabbage, rhubarb and apples without the addition of any extra fat to the food (the average daily fat content of the food was two grams with a maximum of five grams on very rare occasions). Even such a low minimum of fat was sufficient to satisfy the nutritive requirements of vigorous and healthy individuals and, furthermore, furnished all that was necessary to keep them well and vigorous, provided there was a sufficiency of vegetables in the diet.

This matter is of particular importance in emergency circumstances as, for instance, when the feeding of a nation becomes a problem of constructive statesmanship. In the late war with a general shortage of food the principles of dietetics assumed unwonted importance, and the proper appraisal of these fundamental principles meant meeting or avoiding serious consequences. Hindhede is of the opinion that Holland, his native land, was saved from the ravages of famine, while Germany has been the prey of stark starvation, because of their different attitude towards the fundamentals of nutrition. German thought and practice were completely dominated by the Voit nutritional standard of high protein and high fat requirement. To secure this Germany had to sacrifice valuable acreage to raise abundant live stock, while at the same time her population starved for lack

of agricultural products. Holland, on the contrary, concentrated her energy on raising the maximum of potatoes, wheat and vegetables. She, thus, provided for her people a predominantly vegetarian diet which with the addition of dairy products made it possible for them to weather through the bleak and trying years of the war without suffering those appalling consequences which brought physical ruin to the population of Germany. Indeed, by wisely utilizing the productivity of her land, Holland raised crops of potatoes and wheat which actually enabled her to stretch a helping hand to her neighbors besides taking care of her own people.

e. Vitamin Starvation[1]

The discovery of the isodynamy of food stuffs on which dietetics of the last quarter of a century has been built sinks into relative insignificance when one reflects over the startling advance in our knowledge of nutrition achieved in the last few years. The law of isodynamy proclaims that proteins, fats, and carbohydrates represent each a definite, determinable quantity of energy expressed in heat units (calories) and, furthermore, that these food stuffs are interchangeable provided the substitutions yield to the organism an equivalent of energy. The discovery of this important law established dietetics on a solid scientific basis, thus marking a great step forward in the evolution of this branch of physiology. But, at the same time, it exercised a detrimental influence by the over-emphasis it placed on the purely quantitative relationships of food stuffs and forcing the study of nutrition into a narrow, mechanistic rut. The practical value of the theory of isodynamy is, of course, incalculable. It has made possible to arrange the diet of the sick and the well necessary for maintenance or work on a strict and objective basis. But being

[1] The term vitamin has been proposed by Drummond and seems preferable to the nomenclature of other investigators. It is less committal than Funk's original "vitamine" which suggests a definite chemical structure. At the same time, the name which is descriptive of the high importance of these substances is well to retain, especially since common usage has already given to it its sanction. Other terms, like "accessory" substances, "fat-soluble" and "water-soluble" factors, are indefinite and rather cumbersome. "Accessory" may be applied with equal justification to dietary articles which do not share with the vitamins their great nutritional value; while descriptive terms referring to solubility properties are misleading because these are not at all specific. Vitamin A, B and C correspond to "fat-soluble A," "water-soluble B" and antiscorbutic C.

concerned exclusively with the energy yielding food stuffs the theory was bound sooner or later to lead to intellectual stagnation. No further progress could come from that quarter, and, indeed, the newer advance came when instead of the quantitative laws of nutrition the qualitative value of foods irrespective of their energy content became the center of interest and research. The epoch-making discovery of the vitamins belongs to this era of nutritional investigation.

The vitamins as a group are characterized by the remarkable fact that their important function in the economy of the organism is incommensurate with the amount ordinarily consumed. As energy yielders these substances are unquestionably insignificant beyond mention. It is impossible at present to state—in view of our complete ignorance of the chemical nature of the vitamins—whether they owe this tremendous importance to the circumstance that they supply the organism with some specific structural component which the animal is incapable to synthesize, or that they act in the manner of catalysts promoting the complex chemical processes in the body. As in the case of enzymes whose chemical nature has not yet been grasped either, we can judge of the presence, or absence, or insufficiency of the vitamins solely by the result of their action. In other words, the test for vitamins is purely biological. Since we are here concerned with the problem of starvation, only the effect of a lack of vitamin, or vitamin starvation, will be considered. This usually reveals itself in the arrest of growth and progressive loss of weight as well as in a variety of definite pathological conditions which take the form of specific diseases. It is to be noted that while loss of weight is a general inanition effect, the cessation of the growth processes is by no means a result of starvation. It would seem, therefore, that arrest of growth is more or less specific to the partial inanition of vitamins.

The first important step toward the discovery of the vitamins was made when Eijkman showed that the disease beriberi was associated with an exclusive consumption of decorticated or polished rice. Beriberi was never found where the diet consisted of whole rice. This, of course, immediately suggested that there must be something present in the polishings without which the organism fails to retain itself in a healthy condition. Thus the fact was recognized for the first time that a specific disease may be caused by a lack or deficiency of some essential stuff which

must be supplied with the diet. But the true appreciation of the qualitative properties of diets was derived from the now classical researches of Hopkins in which he attempted to rear animals on diet synthesized from highly purified ingredients. Although it is well known that in some respects the animal organism possesses remarkable synthetic ability which is displayed in producing different constituents of the protoplasm, for instance, the complex organic phosphorus compounds, nucleic acids, etc. from simple materials, nevertheless the organism is unable to make its vitamins for which it is entirely dependent upon its supply in the food. The plants are the only producers of vitamins. Herbivorous animals obtain their supply from the vegetation on which they thrive and, in turn, convey these substances to carnivorous animals which use them for their food. The milk of herbivorous animals is likewise a very important source of the different vitamins, and recent research shows that the content of vitamin in the milk is directly dependent on the freshness of their vegetable food.

In summing up the results of his feeding experiments Hopkins came to the general conclusion that animals are not able to live for long on mixtures of pure protein, fat and carbohydrate. Even when the necessary inorganic material is carefully furnished, the animal will still fail to survive for any length of time on a diet of purified food stuffs. Their failure to grow, physical decline and ultimate death were found to be due not to an insufficient intake of food, though more recent studies of the subject make it seem very probable that an absence of vitamins does affect the appetite and, therefore, indirectly lowers the amount of food consumed.

The natural foods of animals consist either of vegetable or animal tissues, which are known to contain a variety of substances beside the proteins, fats and carbohydrates. All of these are essential for the well-being of the organism. Scurvy, beriberi, rickets, and apparently pellagra, are all associated with some nutritive error and are, therefore, more or less amenable to dietetic treatment.

Had Hopkins' experiments done nothing else but establish the fact that the animal organism can not be maintained in good health and in proper functional order on diets synthesized from highly purified materials, their significance would have remained chiefly negative. But Hopkins has gone much further and dis-

covered, on adding small amounts of milk daily (about four per cent of the total quantity of food) to the basal ration consisting of purified caseinogen, starch, cane sugar, lard and inorganic salts, that the rats grew uninterruptedly to normal size. The same startling result was obtained with an extract of the deproteinized and ash-free milk residue as well as by the addition of yeast. The retrieving influence of small quantities of milk was already noted in the earlier experiments of Lunin which were discussed in the previous section. Lunin, experimenting with salt-poor food mixtures, interpreted the nutritive value of the added raw milk as being due to its mineralized organic compounds. This, of course, is entirely erroneous. Lunin based his opinion on the fact that his artificial salt mixture resembling in composition the ash of milk failed to promote growth, as was also found later by Osborne and Mendel who employed an "artificial protein-free milk" consisting of a mixture of lactose and salts. The difference in the biological effect of these milk-like synthetic preparations and of natural milk must, therefore, depend upon the presence in the latter of some substance which our chemical methods have as yet failed to identify and isolate.

The experiments of Hopkins, demonstrating that it is futile to attempt to promote normal growth and to insure the full span of the animal's existence even when the diet provides sufficient building material and energy in the form of standard dietary articles, sounded the death knell of the purely physical conception of nutrition which so long preëmpted the scientific field. They inaugurated a new era whose creative impulse has not spent itself yet and which promises to plant the science of nutrition on a bottom rock foundation with vistas of possibilities for further progress.

Next, and equal in importance to the nutritional studies of Hopkins, are the numerous researches of McCollum and his collaborators. We owe to these investigators the differentiation into two distinct classes of the substances which—apart from mineral matter and energy yielding foods—are indispensable to health, growth and reproduction. First McCollum discovered that by feeding a basic ration consisting of caseinogen, lactose, lard and inorganic salts he failed to secure dietetic conditions favorable to continuous growth of his rats. The animals, however, did not die prematurely on this diet. Of the various things he tried he found the ether extract of egg yolks or of butter to be

the only potent factors in restoring conditions necessary for normal growth by apparently supplying something in which the artificial ration was deficient. This was also corroborated by Osborne and Mendel who definitely proved that the missing factor was derived from the fat fraction of the butter. Because of the fact that this substance was first found associated with fat McCollum designated it as the "fat-soluble" factor. It was already pointed out why this nomenclature should be abolished; it corresponds to vitamin A in accordance with the terminology followed in this discussion.

The vitamin A is found widely distributed in various plants like cabbage, lettuce, spinach, carrots; in the embryo or germ of wheat, maize, rice; it is likewise abundantly present in eggs of all animals. So far as animals are concerned, the vitamin A is to be found principally in such glandular tissues as the liver, pancreas, kidney. Furthermore, certain animal fats, especially those derived from glandular organs like the liver oils (cod-liver oil) and milk fat (hence all such dairy products as butter, cream and cheese) are among the most potent carriers of the vitamin A. It is rather remarkable that oils of vegetable origin with very few exceptions are practically devoid of this vitamin. This fact was recognized by McCollum who was the first to discover that olive oil failed to make his synthetic rations adequate for growth and health as the ether extracts of egg yolk or butter did. Further investigations have led McCollum to conclude that the animal organism contains apparently enough reserve of the vitamin A in its glandular organs to supply its immediate needs when none is furnished with the food. This may perhaps be due to the fact that the vitamin A is relatively speaking very stable. As soon, however, as the reserve present in the organism is exhausted growth is brought to a stop. At the same time the animal, whose appearance up to this time is normal and healthy, begins to give evidence of lowered vitality and of diminished resistance to infection. McCollum observed that the rats which he fed on rations devoid of the vitamin A developed a peculiar eye disease which has since been recognized as a specific affection produced by a lack of this vitamin. The disease, which has been identified as xerophthalmia, manifests itself at first as a simple inflammation of the eyelids, which later spreads to the conjunctiva and soon leads to hemorrhagic and even purulent discharges. The inflammation, if not attended to,

will involve the cornea and finally occasion blindness. Unless the disease has progressed too far the condition can be speedily and effectively remedied by supplying vitamin A, the absence of which is the specific cause for this disease.

It has been pointed out elsewhere in this discussion that malnutrition is commonly accompanied by pathological affections of the eyes, such as night blindness, etc. A condition similar to that discovered by McCollum in his experimental rats has been observed among young children whose food was deficient in the vitamin A. Thus, many years ago, Mori [1] of Japan described an external eye disease, "Hikan," which he found among the children of certain fishing villages. Long before the importance, or even the existence, of vitamins was recognized, Mori traced the disease to faulty dieting, especially to the want of fat in their food. The dietary articles which he employed in the effort to cure this disease and to prevent its occurrence, namely, eel-fat, cod-liver oil, chicken livers, etc. are nowadays recognized as being among the most important sources of the vitamin A. In more recent years Bloch reported a number of cases of ocular diseases in babies artificially fed on separated milk. The affection of the eyes was found to range from mild xerosis of the conjunctiva to such severe conditions with involvement of the cornea which in several of the babies resulted in complete blindness. Clinical treatment of these patients proved of no avail, but a change in the diet with whole milk replacing the separated milk, together with a liberal addition of cod-liver oil, was followed by speedy improvement in the condition of the babies both as to their eyes and to the general state of their health. All the children before the mode of their nutrition had been modified were considerably below the normal standard.

The second vitamin necessary for the normal growth and continued well-being of the animal, the existence of which has likewise been proved by McCollum, has been obtained from the water extract of certain biological materials. It is for this reason that McCollum labeled this substance the "water-soluble" factor, but we shall designate it as the vitamin B. It is absolutely distinct from the vitamin A from which it differs not only by its solubility but also by its physiological properties. The vitamin B is less stable than the vitamin A and the organism has a much smaller reserve. The organism is, therefore, more

[1] *Jahrb. f. Kinderh.*, 59, 175, 1904.

immediately dependent for its supply on the food. Whether because there is less vitamin B present in the tissues of animals or because of its greater degree of lability, the lack of this vitamin in the diet initiates quickly a decline in body weight, brings about nervous incoördination and, finally, death. In discussing the older experiments of Foster, on the effect of food which has been previously extracted with water to remove the salts, it has been argued that the failure of his experimental animals, both pigeons and dogs, to survive on those diets and the fact that they succumb while displaying various paralytic phenomena, did not bear out Foster's thesis that the animals were suffering from mineral starvation. There is no denying that this factor may have played some part in his experiments, but the symptoms he described correspond more nearly to what we now know to be the effect of a deficiency in the vitamin B.

The B like the A vitamin is a product of plant metabolism and the primary source of its supply is in the vegetable tissues. It is present abundantly in yeast (both the dry yeast and the extract), in the embryo or germ of various seeds as well as in eggs of animals. It is also found in large quantity in all cellular vegetable structures like the leaf and fruit. The milk of animals whose food is rich in this vitamin is likewise an important source of the vitamin B. Of the animal tissues the various glandular organs are particularly rich in vitamin B.

So far emphasis has been laid on the effect of vitamin starvation on young, still growing organisms. Here the dietary deficiency manifests itself quickly in the inhibition of the growth process; therefore, the young animal can be used in testing for the presence or absence of vitamins in a diet. The adult organism is subject in no less a degree to the influence of vitamins, though the effect of a deficiency or even total lack develops more slowly causing apparently a disturbance of the general metabolism, which eventually leads to a specific disease with a well defined syndrome. The treatment of the disease is wholly dietary.

A disease which for many years has been known to occur among people living on rice, especially in the tropical regions, has been definitely acknowledged as the effect of a dietary deficiency. This is always connected with rice, milled or polished by modern machinery, which removes from the grain the cortex together with the germ. It has been pointed out already that the germ of seeds contains the vitamin B. The disease, beriberi,

which develops on a diet deficient in this element is a form of peripheral neuritis which may or may not be accompanied by edema, and is generally fatal. Great progress in the treatment of this disease has been made since the discovery was made that the disease is identical with the pathological condition induced in birds (polyneuritis gallinorum) by similar dietetic deficiencies. The disease can also be brought on by diets compounded from substances free from vitamin B, and the administration of this vitamin has a definite therapeutic effect. It is one of the well established facts that the anti-neuritic (or anti-beriberi) substance is identical with the vitamin B of McCollum. The identification of the incidence of beriberi with a vitamin B deficiency has had very important practical results. Natural foods like yeast, germs of various seeds, eggs and glandular tissues of animals all of which are known to contain this vitamin are very effective prophylactic agents, and can also be employed with great success in the treatment of the disease.

Apart from the specific effect of a vitamin A deficiency on the eyes there is little certainty of its pathogenic significance. It has been thought that the edemas prevalent during the war among the people who had little fat in their diet was a vitamin A deficiency disease. The experiments of Kohman, showing that the edema is the product of a complexity of circumstances involving general malnutrition together with a very low protein intake, dispense with this hypothesis. The recent studies undertaken by the English investigators suggested that rickets is probably a vitamin A deficiency disease. We referred already to Herter's experiments with pigs nourished on food exceedingly poor in fat. The evidence from those experiments points more to a development in the pigs of scurvy rather than rickets. The poor development of their bones was obviously due to defective calcification owing to diminished absorption of the calcium phosphate from the alimentary canal. This must, therefore, be regarded as the effect of mineral starvation and not of a vitamin A deficiency. Drummond has shown that the lack of vitamin A does not affect the absorption of fat. Furthermore, he has shown that rats fed on Vitamin A-free rations are capable of synthesizing body fat even from fatty acids. This may perhaps account for the fact that in the experience of the English investigators even vegetable oils which are known to be free from vitamin A exerted a certain beneficial influence in preventing the onset of rickets. This effect

may have been wholly due to better absorption of calcium phosphate, thus preventing poor calcification of the bones. The American students of this problem, both Hess and McCollum with his coworkers, find no evidence for the hypothesis of the relation between rickets and vitamin A starvation. Hess points out that the disease occurs even in infants receiving large quantities of milk with an ample vitamin A supply. Leafy vegetables and cream which are both rich sources of this vitamin, are comparatively ineffective preventives. McCollum, too, fails to show that the lack of vitamin A alone is responsible for the development of rickets. He considers the disease to be caused by a complex dietary deficiency, which involves the calcium and protein factors. Cod-liver oil is the most potent stimulant to growth and is of the greatest therapeutic value in the case of rickets. It is very probable, therefore, that the vitamin A can not be regarded as a specific anti-rachitic factor in the same sense as the vitamin B has been shown to be an anti-neuritic factor.

Our knowledge of the vitamins has been extended in recent years by the addition of a third dietary factor, the vitamin C, which is likewise necessary for normal growth. When it is absent from a diet the animal loses weight. The deficiency of vitamin C is the specific cause of scurvy, a disease which for many years has been known to be due to a dietetic error. The disease has always been one of the most dreaded scourges of seamen and of prison inmates, whose régime is generally unvaried and devoid of fresh food stuffs. Vitamin C is a specific anti-scorbutic agent. Like the vitamins A and B it is most abundant in plant tissues, especially those which are metabolically active. It differs from the other vitamins in that it is the least stable and is destroyed even by mere desiccating of the material containing it. The juice of lemons, oranges, turnip (swede), cabbage and germinated pulses (not the dry) are among the most potent anti-scorbutic dietary articles. Lemon juice has been recognized from the oldest times as an effective corrective of the disease.

Scurvy can be induced experimentally in guinea pigs. The symptoms of guinea pig scurvy are practically the same as in humans suffering from this disease: swelling and tenderness of joints and also of the gums and jaw; hemorrhages in the limbs and not infrequently in the intestinal tract; fracture of bones and loss of teeth. Young guinea pigs whose diet is free from

vitamin C reveal the symptoms of the disease at the age of about 20 days. Unless an attempt at remedying the condition is quickly made, the animals will usually die within two or three weeks. The remedy consists in supplying the missing dietary factor. Fresh vegetables like cabbage or swede and fruits (lemons, oranges, etc.) have the most potent anti-scorbutic effect. Cereals, on the contrary, and such important sources of the A and B vitamins as yeast, eggs and milk are practically of no therapeutic value.

It has been suggested that vitamin C being very labile is found only in plant tissues with an active metabolism as, for instance, leaves and fruits. As it is destroyed by drying it is absent in seeds except when their metabolic activity is restored by germinating.

CHAPTER VI

CHRONIC INANITION

The expression chronic inanition designates a condition generally characterized by underfeeding or undernutrition. It is unlike partial inanition which is ordinarily associated with the lack of some particular component of a normal diet, being strictly speaking a condition of caloric starvation, i.e., the food consumed by the organism not being adequate to furnish the energy which is necessary to maintain the organism's metabolic activity. It is obvious, therefore, that a person, engaged in the performance of heavy work on a dietary allowance which supplies energy for mild tasks only, will be as truly in a state of chronic inanition as is one who through accident, disease or misfortune is obliged to sustain himself on a limited quantity of food. In either event there will be a negative balance between the income and output of energy, a shortage which the organism must make good by infringing slowly but none the less persistently upon its stored reserves. Chronic inanition, or undernutrition, may exist independently of the qualitative composition of the food, which in this respect may be entirely satisfactory. Under the circumstances of famine, owing to a failure of crops, or as it happened during the late war when some of the countries were unable to secure enough food stuffs, especially of a certain kind, the prevalent condition was not that of chronic inanition in the strict sense, but a combination of partial and chronic inanition, the dietaries being deficient both as to quantity and quality. As a social phenomenon, therefore, the underfeeding is rarely if ever of the simple type of caloric starvation, but is of the more complex nature of malnutrition.

While acute fasting, of the protracted kind at any rate, is a relatively rare occurrence, and, from a sociological standpoint, is of little importance, chronic inanition is nearly an everyday event. The person who is unable to take sufficient nourishment because of a diseased condition, and the neurasthenic, who starves himself

systematically haunted by an imaginary fear of dire consequences of eating too much, are well known clinically. But ignorance of the rudiments of nutrition and more especially poverty are the most important causes of undernutrition as a sociological phenomenon. Not only does the workingman, who spends more energy in his labor than his daily bread yields him, starve himself chronically, but whenever the wage earned does not keep pace with the cost of living there is inevitably a lowering of the standard which in physiological terms means underfeeding and physical deterioration, ultimately undermining the working capacity of the wage earner himself and of his family.

Chapin's report of 1909 on the standard of living in workingmen's families, though it deals only with a small portion of the industrial social organization, nevertheless brought to view a deplorable state of affairs in the matter of nutrition of the working population. The degree of undernourishment has been ascertained by an indirect method of calculation based upon the amount of food purchased. This, of course, leaves out of consideration the waste incidental to the process of food preparation. Furthermore, it overlooks entirely the most important question of the quality and variety of the diet. The calculation therefore errs in the direction of underestimating rather than overstating the condition as it existed at that time. The report disclosed that $1,100 per year was then the lowest income which prevented actual undernourishment in a family of five. The proportion of malnourished families according to their income was as follows:

$400–$499	76%
500– 799	32%
800– 899	22%
900–1099	9%

Prolonged fasting for religious purposes, already discussed, assumes likewise a social significance owing to its deleterious effect upon the health of the population. It must be remembered, however, that in all these instances the evil results are to be traced generally to the combined action of a chronic partial inanition.

To appraise the influence of underfeeding as a case of caloric starvation one must resort to the laboratory methods of investigation, where through careful control of conditions one may study the uncomplicated effects of chronic inanition. When one con-

siders the far greater significance of chronic inanition both from the clinical and sociological aspect, it is remarkable that physiologists have given such scant attention to this problem as compared with the volume of research directed to the study of acute inanition.

The interest aroused by the subject of chronic inanition must be traced to a fundamental theoretical consideration as to whether or not the basal metabolism of the organism is modifiable and adjustable to the amount of nutriment consumed. In other words, whether or not the energy expenditure of the organism is graded according to the energy income which it obtains with its food.

By basal metabolism is meant the expenditure of energy involved in maintaining the essential physiological functions, such as the activity of the heart, lungs, nervous system, etc., which are, of course, all subsidiary to the life processes of the ultimate cellular elements of the organism. The basal metabolism is a fairly fixed quantity characteristic for the organism or even a group of similar organisms. Basal metabolism is, therefore, clearly distinguishable from the metabolic activity associated with two functions, muscular work and the work of digestion, which are the greatest consumers of caloric energy. This part of the organism's metabolism, especially that occasioned by muscular exertion, is an extremely variable quantity and is superimposed, so to speak, on the basal metabolism. In the previous discussion of the chemical phenomena of acute inanition it was pointed out that the fasting organism's basal metabolism readjusts itself to a lower grade. Following a transitional period, the basal metabolism establishes itself at a definite level considerably lower than that typical for the normal animal. At this level the metabolism maintains itself practically constant during the greater part of the fast in spite of the continuously declining body weight. The question naturally arose, whether an organism subsisting on a limited diet, or on a diet actually below the minimum requirement, would adjust itself in a similar manner by reducing its basal metabolism. In other words, does an organism which is chronically underfed through accident, disease, or necessity live more sparingly? Clinical studies made by Klemperer, Svenson, Magnus-Levy recognized the possibility, though they did not prove conclusively that the metabolic activity of the body of their patients readjusts itself to low or high

caloric diets. Klemperer cites the case of a seamstress who, while resting in bed, subsisted on only 18 Calories per kilogram of body weight per 24 hours. This is considerably below the metabolic level of a normally nourished individual. It is well to recall here also that Richet found in the case of hysterical patients that their metabolic exchange was 12.6 and 8.7 Calories per kilogram and per 24 hours respectively, and with food barely sufficient to furnish that amount of energy they sustained a very insignificant loss in body weight.

Castaldi, who spent many months in Austria as a war prisoner, states that "the organism adapts itself remarkably to an unaccustomed diet." At what price, however, this readjustment takes place we find out from the further information furnished by this author. In one concentration camp the daily food averaged only 1,300 Calories, and Castaldi suffered from anemia and reduced capacity for both physical and mental exertion; his memory in particular was impaired. On being transferred to the prison at Bishitz, where he received 1,800 to 1,900 Calories per day, he soon recuperated and reached a stable balance.

One of the earliest attempts to investigate this problem by laboratory methods was that of J. A. Pashutin who in 1895 published the results of his experiments on animals kept on reduced diets. He observed that during the period of underfeeding both the oxygen consumption and carbon dioxide production were appreciably lower. With one dog, for instance, the food was reduced to half the normal quantity. The reduction was made gradually, the entire experiment extending over a period of 87 days. At the closing of the experiment with varying degrees of underfeeding the body weight was only 13 per cent less than at the start. In the meantime, the gaseous metabolism also diminished, the oxygen consumption being reduced to 95 per cent and the carbon dioxide production to 80.

In 1911 the author undertook a similar investigation under the direction of the late Professor Zuntz, and in the following year conducted a carefully planned investigation with another dog in the Carnegie Nutrition laboratory. The results of this last investigation have hitherto been published only in the form of preliminary reports.

The subject of these experiments, a vigorous Airedale dog, was kept in a metabolism cage throughout the entire duration of the investigation, which permitted maintaining constant environ-

mental conditions. The dog was fed regularly at a definite hour each morning soon after the rectal temperature and the weight had been determined. From time to time respiration experiments were performed with the dog in the closed circuit apparatus of Benedict's construction. The animal was previously carefully trained to stay quietly in the box of the apparatus. The respiration experiments were usually made at 20 to 21° C., which temperature was found most favorable to the animal's restfulness. The respiration experiments were performed invariably 24 hours after the last feeding so that the metabolic activity was not complicated by post-absorptive phenomena. The conditions of experimentation were maintained uniform throughout the entire series and the results are, therefore, all strictly comparable. Each respiration experiment was made up of several thirty-minute periods. The behavior of the animal during the experiment was automatically recorded and only such periods were utilized, the graphic record of which showed that the animal kept very quiet.

During a preliminary period of ten days three respiration experiments were performed, and with the aid of the data so determined the normal basal metabolism of the dog was established. It was found that the dog produced on the average 3.75 liters of carbon dioxide and consumed 4.76 of oxygen per hour. This gaseous exchange (at the prevailing respiratory quotient of 0.79) is equivalent to an energy output of 546 Calories of heat per day, or 39.3 Calories per kilogram of body weight per 24 hours.

As can be seen from the accompanying table and chart on pages 266 and 267, the dog received at this time 987 Calories daily with the food which consisted of ground meat, rice and lard. Although the dog was confined to the metabolism cage and could not, therefore, spend much energy in muscular exertion, the excess of 75 per cent over the minimum requirement was apparently just sufficient to maintain a state of physiological equilibrium, the dog retaining practically a constant weight.

At the close of this ten-day preliminary period the diet was reduced to about one-third (36.3%). On this basis of limited rationing the dog received 25.7 Calories instead of 70.8 per kilogram during the first week of underfeeding. At the end of the experiment, nine weeks later, when the weight of the dog diminished from 13.94 to 8.04 kilograms, the food supplied 40.3 Calories per kilogram, or 57 per cent of the original diet. In the

TABLE IX

Condition of Dog	Duration of Period	Average per Day: Body Weight in Kg.	Rectal Temper. °C.	Respiration Rate per Minute	Pulse Rate per Minute	Nitrogen Intake Gm.	Water Ccm.	Urine Ccm.	Nitrogen in Urine Gm.	Feces: Dry Matter Gm.	Feces: Nitrogen Gm.	Nitrogen Eliminated Gm.	Nitrogen Balance	Calories in Food	Respiratory Exchange: CO_2 per Hour	O_2 per Hour	Respiratory Quotient	Average Pulse Rate	Basal Metabolism, Calories per Day
															Lit.	Lit.			
Normal	10 days	13.94	38.0	12	53.7	9.33	629	498	7.188	3.587	0.2[illegible]8	7.396	+1.934	987	3.75	4.76	0.79	47.5	546
Underfeeding	1st wk.	13.59	37.6			3.10	360	412	5.291	3.267	0.160	5.351	—2.251	349	3.16	4.36	0.73	43.4	493
	2nd "	12.79	37.6			3.10	369	355	4.721	3.501	0.197	4.918	—1.818	349	3.01	4.03	0.75	41.7	458
	3rd "	12.17	37.3	9	36	3.10	425	408	4.690	3.320	0.179	4.869	—1.769	349	2.99	4.01	0.75	44.6	457
	4th "	11.59	36.9			3.243	463	443	5.143	1.616	0.093	5.236	—1.993	327	3.00	3.94	0.76	42.3	449
	5th "	11.02	36.7			3.30	534	469	5.281	3.420	0.169	5.430	—2.130	310	2.89	3.80	0.76	44.1	433
	6th "	10.38	36.7			3.30	497	489	6.109	3.210	0.203	6.312	—3.012	310	2.87	3.90	0.74	45.9	442
	7th "	9.70	36.4			3.30	451	445	6.114	2.987	0.149	6.263	—2.963	310	2.99	4.04	0.74	52.2	454
	8th "	8.92	35.5	6	31	3.283	414	433	7.450	2.843	0.153	7.603	—4.320	313	2.59	3.41	0.76	56.1	417
	9th "	8.27	35.0	6	41*	3.180	419	416	6.081	1.680	0.090	6.171	—2.991	333	2.39 2.54	3.07 3.01	0.78 0.84	51.2 60.9	369 350*
Refeeding	1st wk.	8.77	38.4	10 14	60 72	15.623	879	619	8.654	13.136	0.781	9.435	+6.188	1572	2.69 3.63	3.30 4.92	0.81 0.74	68.0 79.3	381 558
	2nd "	10.44	38.0		62.6	21.471	1044	806	12.184	11.474	0.767	12.951	+8.520	1781	4.90	6.42	0.76	78.6	718
	3rd "	12.38	38.0			23.890	1135	853	14.689	10.448	0.767	15.456	+8.434	1890	4.46 4.31	5.51 5.18	0.81 0.83	70.5 72.4	637 603
	4th "	13.64	37.8		56	20.276	1080	863	14.203	13.234	1.033	15.236	+5.040	1740	3.89	5.21	0.75	64.6	593

* Last day of underfeeding.

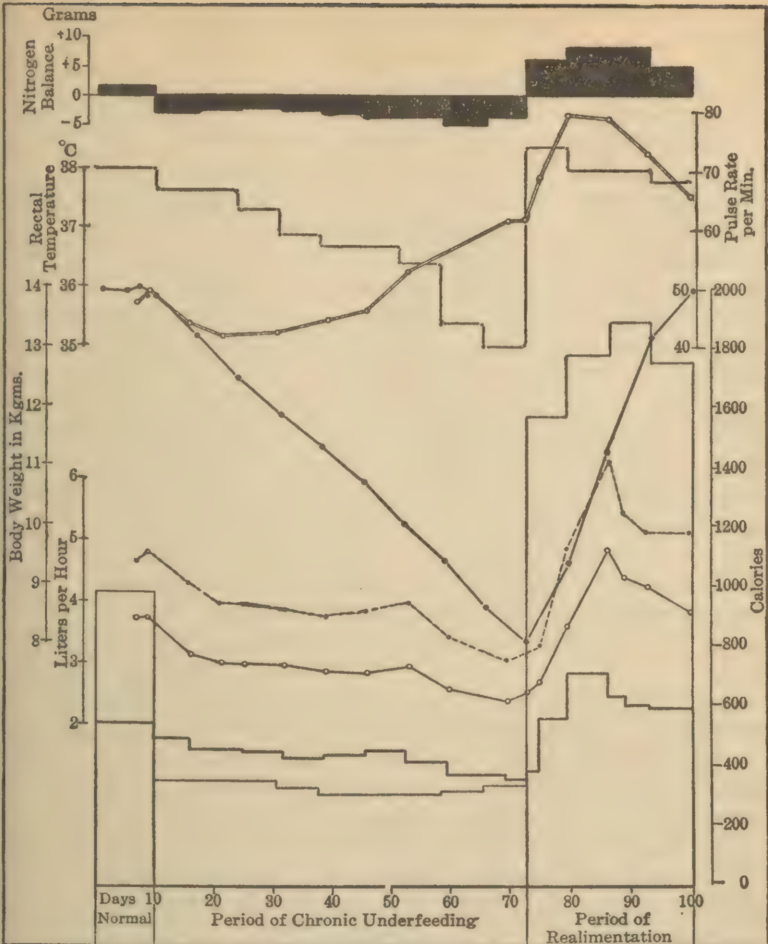

FIGURE 11.—Graphic representation of the experimental data obtained with a dog during a period of chronic undernutrition and of subsequent over-nutrition. The calorific value of the daily diet is shown by rectangles drawn in light lines, while the basal metabolism of the animal, calculated from the respiration experiments, is superimposed upon the former and is shown by rectangles drawn in heavy lines. The carbon dioxide produced and the oxygen consumed per hour are represented by the continuous and by the dash-line curves respectively. The nitrogen balance of the dog (*i.e.*, the difference between the amount given in the food and the amount excreted in the daily urine) at the different periods of the experiment is represented at the top of the chart by the shaded areas, those above the zero line indicating a positive balance, the dog retaining nitrogen, and those below the line representing the amount of nitrogen lost from the organism. The changes in body weight are shown in the heavy line curve, while the variations in the rate of the heart beat and of the rectal temperature are represented by a double and by a single fine line curve respectively. (Based on Morgulis' data.)

meantime the composition of the food remained the same, but in place of 250 grams of meat, 50 of lard and 35 of rice, the daily quantities were now only 90, 15 and 15 grams respectively. It will be noted that the energy content of the food was actually less than the minimum, or basal, requirement of the dog. The deficiency, however, which at the commencement of underfeeding was 40 per cent of the basal metabolism, has gradually decreased to only 8 per cent with the progress of the experiment. The dog nevertheless continued losing weight, i.e., was consuming its own substance, at a remarkably uniform rate during the entire experimental period, as may be seen from the weight curve in the chart. It seems obvious, therefore, that a supply of energy which was inadequate for our dog when his weight was 14 kilograms was equally inadequate when his body weight was reduced to only 8 kilograms. This is an important fact, because it goes to show that the animal reacts not as a "mosaic" of kilograms, but as a biological entity. It is undoubtedly convenient to calculate the metabolism on the basis of a standard unit of body weight, but the metabolic activity of the individual must be considered in its entirety, a point of view which will enable to interpret intelligently the results.

A respiration experiment performed on the fifth day of underfeeding already reveals a remarkable change in the basal metabolism. The carbon dioxide produced per hour decreased to 3.16 liters, i.e., almost 17 per cent less than under the condition of adequate rationing. The oxygen consumption also diminished 10 per cent, so that even at this early stage of the chronic underfeeding the intensity of the metabolic activity is noticeably reduced. A week later it decreased still further, to 3.01 liters of carbon dioxide and 4.03 of oxygen per hour. The total minimum energy requirement of the dog has meanwhile become 458 Calories, or nearly 16 per cent less than in the preliminary period when the dog received a full diet. At that time the body weight diminished about 8.5 per cent.

The gradual decrease in the respiratory exchange can be best encompassed by examining the actual data given in the table as well as in the chart, Figure 11. Practically no change occurs from now until the end of the seventh week of chronic inanition when the body weight has already declined 30 per cent. The basal metabolism, having fallen about 25 per cent below the normal, remains at this low level. But in the eighth week of

the underfeeding, when the dog lost more than 30 per cent of his weight, a new and abrupt decline takes place in the metabolic activity. Both the carbon dioxide production and the oxygen consumption dropped off suddenly 10 per cent, being now 2.59 and 3.41 liters per hour respectively. The basal metabolism of the animal has thus diminished over 30 per cent.

It was already pointed out that the basal metabolism, as soon as the régime of chronic starvation began, suffered an abrupt decrease, but a more or less constant level was very soon reached where it remained—with slight fluctuations—for several weeks. The second abrupt drop in the metabolic activity at an advanced time in the experiment must be regarded as the starting point of a third stage which physiologically is different from the previous. This is substantiated also by the observation that signs of physical debility appear at this time and the body temperature falls off very rapidly. The debility which ensues in the eighth week of underfeeding is rather remarkable because dogs subjected to complete fasting, even without water, often betray no debility until almost the last few hours before death from starvation. In view of this fact it is worthy of special comment, and subsequently we shall refer to this again, that when the body weight has fallen only a little over 30 per cent the dog subsisting on short rations was so weak that he had to be taken out from and carried back into the cage. An experiment performed on the sixty-second day of underfeeding—the weight of the body having diminished 41 per cent—showed that the dog eliminated now but 2.39 liters of carbon dioxide and used up 3.07 of oxygen per hour. The basal metabolism has, compared to the normal level, diminished by nearly 40 per cent. We note, therefore, that under the condition of chronic inanition the basal metabolism passes through the same distinct stages which were recognized in the case of acute inanition.

A study of the temperature curve is instructive. Almost immediately upon cutting down the daily ration to below the minimum requirement of the dog, the rectal temperature commenced to fall off, at first slowly, then more abruptly, and during the last several days of insufficient nourishment, when the condition of the dog was generally very poor, the temperature reached the lowest mark, 34.9° C. This represents a total diminution by three degrees, but whereas the temperature declined one and a half degree in the course of the first 50 days, it

decreased to the same extent within the last two weeks, when the basal metabolism likewise dropped off abruptly.

During each respiration experiment the frequency of the heart beat of the animal was determined over periods extending for several minutes. This was done by means of a stethoscope attached to the dog's body directly over the heart, the transmitting tube passing to the outside of the apparatus. In this way a record of the pulse was made with the animal inside the respiration box. Besides, the pulse rate and the respiration rate were observed at different times during the experiment with the object of determining the minimum rate. The observations were made under the following conditions: The dog was placed on a mattress, covered with a blanket, and every effort made to induce a state of complete relaxation and restfulness. Even the least noise would interfere with the attainment of this object and had to be guarded against. The pulse, as well as the respirations, were counted until a minimum rate was found which did not change for several minutes.

From a number of such observations it was ascertained that during the preliminary period, while the dog was still receiving a sufficient diet, the average pulse rate per minute was 53.7 and that of respiration 12, determined 24 hours after the last feeding. When the dog had been on the reduced diet for about two weeks, the pulse rate at complete rest was 36 per minute and that of respiration 9. At the end of eight weeks of chronic undernutrition the pulse rate was reduced to 30 to 32, while the respiration was reduced to 6 per minute. Only in the last days of the experiment did the pulse rate increase. At this time the smallest number of beats counted in the course of several minutes was 41. At the same time, it will be recalled, the animal was already in a state of exhaustion and was unable to get on a bench or into the cage without assistance. The heart beat became also irregular and weak, and the sounds lost their clear resonance. It is possible that the increased frequency of the heart beat is an attempt of the circulation to compensate the great falling off in blood pressure which, in a previous section, has been shown to occur in advanced stages of inanition.

In the table and in the chart will be found records of the pulse rate observed during the experiments in the respiration apparatus. Following an initial reduction in rate from an average of 47.5 per minute, which existed in the preliminary period, the rate of

the heart beat (with slight fluctuations) remained practically constant (41.7 to 45.9) during that part of the experiment which is characterized by a relative stability of the basal metabolism at a reduced level. But in the last two or three weeks, and while the basal metabolism suffers a further reduction from its previous low level, the pulse rate increases markedly and exceeds even the normal rate (52.2 to 60.9). These observations, therefore, tally with the observations made on the dog outside the respiration apparatus.

An examination of the respiratory quotients in successive metabolism experiments reveals the interesting fact that with the progress of the chronic inanition there is a tendency for the quotients to rise. This tendency becomes particularly noticeable within the last week when the basal metabolism has already fallen to a very low level (about 64% of the normal). In acute fasting the tendency is for the respiratory quotients to diminish. The contrast between the acute and chronic inanition as regards the effect upon the respiratory quotient is, therefore, most marked. The cause of this difference is obvious. In acute fasting, when the animal depends entirely on its own reserves for the sources of energy, the carbohydrate stored in the tissues is very rapidly used up, and subsequently the combustion which yields heat to the body is principally that of fat and protein. But in the state of chronic inanition part of the energy requirement, at any rate, is supplied, and with enough of carbohydrate in the food the quantity of carbohydrate deposited in the tissues is not seriously affected. A study of the non-protein respiratory quotients [1] shows that the organism is very sparing with its carbohydrate except in the most advanced stage of the underfeeding. At that time the calories furnished by the combustion of fat rapidly decreases while the carbohydrate moiety assumes a progressively increasing importance. This, of course, accounts for the fact that the respiratory quotients are relatively high especially in the ninth week, when the fat depots are seriously depleted.

Besides the gaseous metabolism, the nitrogen excretion through urine and feces has been regularly determined. During the preliminary period the nitrogen balance was determined for two

[1] After deducing the carbon dioxide production and the oxygen consumption coincident with the urinary nitrogen excretion for the same period the ratio between the balance of carbon dioxide and oxygen indicates the relative proportions of fat and carbohydrate partaking in the metabolic exchange, and is designated the "non-protein respiratory quotient."

five-day intervals. In the first five days the dog received in his food 48.8 grams of nitrogen, and excreted in the urine 37.98 grams. Considering also the nitrogen lost with the feces there was a retention of 9.8 grams of nitrogen. In the next five-day interval the dog retained 9.54 grams of nitrogen. With a total supply of nitrogen in the food of 0.67 gram per kilogram of weight the dog acquired 19.34 grams in ten days, or 1.934 grams per day. This amount was, therefore, more than sufficient to maintain the nitrogen equilibrium, and may have been due perhaps to a lower level of nutrition prior to the experiment. In the chart the nitrogen intake at various times is shown graphically, the nitrogen balance represented by the shaded area indicating the average gain or loss of nitrogen according to its position above or below the base line.

During the period of underfeeding, when the quantity of the food was cut down to one-third, the diet was naturally poor in nitrogen. In the first week of underfeeding the nitrogen was reduced to 0.23 gram per kilogram. This allowance was entirely inadequate and the dog was consuming its own tissues, so that throughout the entire experiment a considerable loss of nitrogen occurred. A glance at the chart will show that with a uniformly low nitrogen intake the daily loss of nitrogen remains fairly constant for about six weeks of underfeeding. The destruction of nitrogenous tissue, however, begins to increase and reaches a maximum in the eighth week. This enhanced elimination of nitrogenous material is undoubtedly associated with the general exhaustion of the fat depot, and coincides in time with the abrupt fall in basal metabolism which marks the initiation of the last and most advanced stage of the underfeeding.

On the basis of Voit's data of the composition of a normal and starved dog we can compute that the dog used for this experiment possessed in the beginning 6.48 kilograms (46.5%) of muscles, but only 2.77 kilograms (34.4%) at the end of the underfeeding. In other words, the dog consumed about 3.71 kilograms of muscle tissue, yielding 118.7 grams of nitrogen. Since the cumulative nitrogen loss was altogether 162.7 grams, 44, or approximately 25 per cent of the total loss, must have been derived from other tissues, particularly the viscera. With the aid of Voit's figures the loss of the viscera can be estimated as being 1.9 kilogram, thus giving, together with the loss sustained by the musculature, a total reduction by 5.61 kilograms, which is only

290 grams less than the observed loss in weight. Of course, even this does not represent a real discrepancy inasmuch as other organs, the bones, etc. also suffered a certain reduction in weight.

Although the influence of the underfeeding has been our chief concern, the study of the subsequent recuperation has such important bearing as to merit discussion here. The truly remarkable changes in the weight and body temperature which ensue immediately with the resumption of abundant feeding can be readily appreciated from the curves in the chart. This period is one of reconvalescence, because the preceding long continued underfeeding enfeebled the dog and impaired his health; his temperature went down to an unusually low level, the heart became weak and irregular, the emaciation was extreme. As soon, however, as abundant feeding was resorted to, a train of most remarkable changes followed leading ultimately to the restoration of the normal condition.

Maintaining precisely the same environmental conditions as before, a respiration experiment was performed on the third day of liberal feeding. The basal metabolism already showed a distinct increase, the carbon dioxide production and oxygen consumption being now 2.69 and 3.30 liters per hour respectively. At the end of one week these have already become 3.63 and 4.92 liters per hour. At this time the minimum metabolism was practically the same as in the preliminary period. But the second week witnessed the highest intensity of the metabolic activity. The carbon dioxide given off was 4.90 and the oxygen consumed was 6.42 liters per hour. If it is recalled that all these respiration experiments were performed on the dog twenty-four hours after the last feeding, it is significant that in two weeks of overfeeding the basal metabolism rose 100 per cent over that in the last stage of underfeeding, and exceeded the normal established during the preliminary period by more than 30 per cent. Unfortunately these experiments give no clue as to the degree of influence which the great influx of nitrogenous material at this time may have had on the metabolic activity. There is, of course, good ground for believing that nitrogenous substances exercise a strong stimulating effect upon the metabolic processes.

Having attained a climax in the second week of re-alimentation, the basal metabolism begins henceforth to decline, as an examination of the quantities of carbon dioxide and oxygen shows. The total minimum metabolism thus tends to return to the

normal level again, and when the initial weight has been restored it is only 9 per cent higher than before the underfeeding began. The recovery of the physical strength, however, proceeds much slower. In a fortnight the external appearance of the dog has changed so completely that it did not seem credible that it was the same dog. The effect upon the muscles and nervous system, however, was more deeply seated and until well in the third week of reconvalescence the dog was still unable to get into the cage without help. But at the end of four weeks the recovery was complete.

Throwing a bird's-eye view over the data obtained for the period of reconvalescence, we note a rapid rise and fall in metabolism of the dog but nothing like an adaptation of the organism to a higher plane of metabolic activity in response to a superfluous inflow of food. The metabolism temporarily rises because the organism at first grows rapidly and consumes material with great avidity. The growth of the dog is most intense at the time the metabolic activity is at its height. As the normal weight is gradually regained, and the growth processes slow down, the basal metabolism likewise readjusts itself to the original plane. The behavior of the temperature, the rate of the pulse and respiration, and the metabolic processes in general, all show this trend to return to the same condition which was characteristic for the dog at the start.

The fundamental problem which the laboratory study of chronic inanition attempts to solve is equally important to the clinician and to the sociologist. Among our poorer classes parsimony is frequently practised to the point of danger. Chronic undernourishment is incompatible with full enjoyment of life, which deprives the individual of his rightful share of happiness. It also lowers his capacity as a producer and thus becomes a social evil. To the clinician the question is of utmost importance because he is confronted by patients whose ailment is very often complicated, if not actually occasioned, by persistent underfeeding. Various gastric abnormalities as well as intestinal troubles, anemia and a number of neuroses may arise from habitual undernourishment. The appreciation of this fact, and a thorough understanding of the physiological effects of chronic inanition, is indispensable in his daily practice.

Our observation that the chronically underfed dog became debilitated in a measure not commonly noted in animals which

undergo a straight fast is also borne out by the more extensive study of this matter by Benedict, Miles, Roth and Smith. These experiments were carried out with two large squads of young men who have been maintained on a reduced diet for about four months. The men in both squads lost a considerable amount of nitrogen from their body reserves, and their weight declined 10 per cent. The intake of Calories normally must have been close to 4,000 per day, but during the experimental time this was only about 2,000. The nitrogen in the daily food, though subject to considerable fluctuation, was not low. But in spite of the ample supply, which was on the average 10.5 grams per day, the nitrogen elimination in the urine had been remarkably constant, and the loss from the body continuous. In this respect also the results agree with those found in the experiment with the chronically starved dog. The systolic, diastolic and pulse pressure of the subjects of the human experiment show a continual decline until a constant body weight at a low plane is established (— 10%). Various careful tests of neuromuscular processes, such as the number of finger movements performed in 10 seconds or the time required for the eye movement through an arc of 40°, which are sound tests of motor coördination, betray a general and unmistakable depression coincident with the subsistence on a régime of insufficient caloric value. The unfavorable effect of this prolonged undernutrition produced even more subtle and far-reaching results. "Judging superficially from the appearance of the men at the end of their long period of restricted diet and from the amount of their intellectual and physical activity, one could assert almost with certainty that a reduction of total caloric intake of one-third was an assured possibility. Certain objections to this are * * * the picture of secondary anemia, marked repression of all normal sex expression, mental unrest and dissatisfaction." And further, the authors give some more testimony of the dangers which lurk in a curtailment of the diet below the necessary requirement: "Protein curtailment is an assured and physiologically sound procedure, and a reduction in calories is possible for long periods, *but definite and significant disturbances of blood composition, normal sex expression, neuro-muscular efficiency and the appearance of mental and physical unrest are deterrent factors.*"

Of the greatest evils incident to the European War the extensive spread of chronic undernutrition should be mentioned.

This was especially true among the people of the Central Powers. Already in the winter of 1916–17, as a result of the perfecting of the blockade, Germany was unable to provide her population with sufficient food, only about two-thirds of the Calories and three-fifths of the protein essential for this purpose being available. The consequence of this enforced chronic inanition was the very general reduction of the body weight of the people below standard (about 20% less).

The diminished *libido sexualis* of the undernourished men has been commented upon by various German authorities who also noted that the war diet was responsible for the cessation of menses among a large number of women. The observations correspond with the general laboratory findings.

In this connection Leo Loeb's investigation on the effect of chronic undernourishment on the sexual cycle in the guinea pig may be recalled. The weight of the animals was reduced 20 to 30 per cent. An examination of the ovaries at that time has revealed atrophic changes in the epithelial elements of the follicles (granulosa), the connective tissue being more resistant to the influence of the underfeeding. No mature follicles have developed under the circumstances, while the hypotypical condition of the ovaries was entirely incompatible with ovulation and the normal course of the sexual cycle.

Reynolds and Macomber have reproduced the "war diet" by feeding animals on foods poor in calcium and in protein, or poor in vitamins and have observed a partial or complete loss of sterility developing as a result of this dietetic régime. It is well to bear in mind, however, that the relation of diet to fecundity may be quite different from that suggested by these experimental results. At any rate Miss Mitchel's observation that the addition of agar to such defective diets may greatly alter the effects on fecundity should not be overlooked. It seems not improbable that the condition recorded by Reynolds and Macomber is not a simple inanition effect.[1]

The wide-spread condition of chronic inanition affecting as it

[1] Since the above has been written two important contributions have appeared which merit special mention in view of their essential bearing upon this question. Evans and Bishop discovered that a diet deficient in vitamin A causes a prolongation of the oestrous changes and failure of ovulation in rats. The disturbance is highly characteristic and is different from that occasioned by any other nutritive deficiency. Meyerstein's results of his histological investigation are corroborative.

did millions of persons at one time naturally aroused the attention of students of nutritional problems. The most important series of experiments is the one which Zuntz and Loewy conducted upon themselves in Berlin. For many years these two prominent scientists kept a record of their metabolism, which thus furnished an excellent basis for comparison. Up to his sixty-third year, i.e., for 22 years, Zuntz's body weight has undergone very little change (it slowly increased about 3 kgms.) while his metabolic activity remained practically unchanged. From personal knowledge of Professor Zuntz, with whom it was my privilege to be associated during 1911, when he was already in his sixty-fifth year, he was a vigorous man and indefatigable worker, equal in endurance and certainly equal in mental alacrity to the much younger men by whom he was surrounded.

As a result of chronic undernutrition during the war he has suffered in common with the rest of the German population. By 1917 he had lost nine kilograms in weight and at the same time his metabolism which had been constant for nearly a quarter of a century had fallen to a lower level. From 1888 until 1910 his metabolic activity per day and square meter of body surface ranged between the narrow limits of 773 and 804 Calories. But in 1916–17 this had already dropped to as low as 709 to 723 Calories. Loewy's experiment tells the selfsame story.

Long continued undernourishment leads to the development of a dropsical condition of the tissues, and in the war-stricken countries this was such a common occurrence that it became known as "war edema." The swelling of the body of famine sufferers is a very well-known fact and is of the same origin. Many of those affected by this disease die. Various explanations have been offered for the development of the edema, such as the predominance of carbohydrates in the diet, excessive ingestion of sodium chloride, or a lack of some essential vitamin. But from the most carefully made studies of Kohman it is obvious that this condition is brought on exclusively by a chronically insufficient diet which is also very deficient in its protein content. The disease is amenable to proper dietetic treatment.

To return, however, to the original problem it may be asked, how far can the diet of a patient, who for some cause or other cannot consume sufficient food, be reduced with impunity? Will the requirement for nourishment adapt itself sufficiently to the reduced diet until the time of stress is past? And with an

adequate caloric supply, can a rational system of dieting be devised that will enable the organism to tide over the temporary vicissitudes? These are some of the problems which must still wait for a satisfactory solution. Now we shall limit the discussion to the effect upon the basal metabolism.

Voit, Müller, von Noorden, and others believe that in cases of nutritional disorders produced by disease the oxidation of substances of the body becomes somewhat more sparing. There has been, however, no positive demonstration of the diminution of metabolic activity as a result of adaptation until the matter was submitted to careful laboratory investigation. It has been shown in the preceding that the basal metabolism of the dog readjusted itself rapidly to the smaller intake of food. Within two weeks of chronic undernutrition the basal metabolism dropped off to a lower plane, and although the weight of the dog still continued to decrease the metabolic activity remained practically stationary until symptoms of physical exhaustion began to develop owing to the persistent underfeeding. From a practical standpoint, it would be very important to know whether with a properly selected diet this low plane of metabolism could be maintained permanently or, at any rate, for a long time, and its effect in the long run. What is the cause of the reduction in metabolic activity? There seem to be two possibilities open: either the depression is due to a reduction of the active protoplasmic mass of the organism as a result of a loss in body weight, or it may be due to the fact that the organism rids itself of the excess of nitrogenous materials with which its body fluids are surcharged. The former hypothesis is hard to accept even when Benedict's modification of it is considered, namely, that with a general reduction of the total active mass of the organism less work will be required even for the fundamental functions of respiration and circulation. This view can be objected to on the following grounds. In the first place, the greatest reduction in metabolic activity does not coincide with the greatest loss of body substance. On the contrary, the basal metabolism becomes established at a lower plane when the body has lost less than 10 per cent. It remains practically unchanged while the animal continues uninterruptedly to lose weight. There seems, however, much to favor the assumption that the reduction in the intake of food produces a proportionately "great reduction of the energy demands for work other than basal maintenance." The results with the dog

would likewise corroborate this view, though on evidence which is indirect. If one calculates from the data of nitrogen elimination and the gaseous exchange the relative amounts of fat, carbohydrate and protein katabolized, allowing an excess of 75 per cent over the minimum requirement (which in the preliminary period was found necessary to secure physiological equilibrium), the calculated body loss is invariably greater than the actually observed loss. The only explanation for this discrepancy is that during the underfeeding a smaller excess of energy is needed for the purpose than during normal feeding.

Thompson and Mendel, from their study of the effects of underfeeding on albino mice, reached the conclusion that in all cases of maintenance there was "a gradual decrease in the amount of food per unit of body weight required to maintain the same weight." This view is generally shared by other investigators of this problem.

The other hypothesis of the reduction of the metabolism in response to a freeing of the system of excessive quantities of dissolved nitrogenous substances still lacks the essential proof of experiment, but the well recognized stimulating effect of nitrogenous material upon the metabolic activity is strong presumptive evidence in its favor. Besides, on this hypothesis we can account for an initial falling off of the basal metabolism, and its subsequent relative stability regardless of a continuously diminishing body weight.

Fortunately, the effects of underfeeding can be quickly effaced when the organism is given a liberal diet. The recovery of our dog was most remarkable. The young men on whom Benedict experimented likewise regained all they had lost during the period of underfeeding and in fact had all attained greater body weight than they possessed before the experiment as soon as they were once more allowed a full ration. Does the metabolic activity adapt itself to an oversupply of nourishment? In this connection it is necessary to distinguish two conditions. First, when an organism can actually grow and form new tissues; second, when an oversupply of nourishment conduces only to an accumulation of reserve material. The first condition is found in young individuals, whose growth has not yet reached its normal termination, or in individuals who have gone through a devastating disease or an experience of inanition. The second condition exists where the normal course of metabolic activity has been undisturbed by

any vicissitude. During the period of excessive feeding the metabolic activity of our dog is very elastic, changing constantly and reflecting in an unmistakable manner the whole gamut of intensities of the protoplasmic activity in the process of reconstruction. An increase in body substance, which under conditions of normal growth of the individual requires months and possibly even years, is accomplished here in a most spectacular manner within the brief span of four weeks. The nitrogen retention in these four weeks exceeds its loss during the nine weeks of chronic inanition. The regenerative processes are extremely vigorous; every cell is tuned up to the highest pitch of activity, and correspondingly there is a rapid rise in the basal metabolism.

There is no valid reason for regarding this increase in metabolism as an adaptive response of the organism to the influx of great quantities of food stuffs, though, of course, the excessive amount of nitrogenous material may perhaps have contributed partly to the stimulation of metabolism. But the basal metabolic activity rises and declines together with the general growth activity of the body. When, however, the work of regeneration is nearly complete, though the supply of nourishment is still greatly in excess of the dog's actual needs, the basal metabolism tends to return to the same level which was characteristic for this animal at the start. It is therefore extremely doubtful if the storing up of reserve material as a result of feeding with superfluous quantities affects the metabolism.

The theory that overfeeding conduces to "luxus consumption" is untenable, and Grafe's exposition of the theory is weak and unconvincing. It is indeed a singular thing that the dog which Grafe and Graham experimented on lost 25 per cent of its weight in a fast of 21 days, but in spite of the fact that for two months subsequently the animal received excessive quantities of food for two months there was no increase in weight beyond the original level of 20 kilograms. Three factors may be considered responsible for this condition. Either the organism lost water in sufficient quantity to counterbalance the retention of solid material, or the dog may have been unusually restless and naturally katabolized great quantities of body substance, or, finally, the basal metabolism of the dog may have been raised to a higher plane. The first possibility Grafe dismisses as incongruous, especially as the analysis of the dog at the closing of the experiment gives no evidence for it. The second possibility Grafe neglects,

or at any rate underestimates, too readily. He is thereby forced to postulate the existence of a higher grade of metabolic function under the condition of overfeeding.

A careful examination of his experimental data fails completely to sustain Grafe's contention. On the contrary it shows the interpretation to be erroneous. The total income of net Calories in the course of 66 days of overfeeding was 124,900, or 1,893 per day. Accepting Grafe's estimate of the minimum energy requirement as 823 Calories, there is still a huge surplus of supply over actual need of 130 per cent. From the 12 respiration experiments performed with the dog the daily energy output was found to be 980 Calories per day, or 20 per cent above the presumed minimum. Supposing, however, that the daily energy output was in round numbers 1,000 Calories, there is still an excess of 59,000 to be accounted for. Supposing, further, that while the animal was in the cellar, where the temperature (15° C.) was lower than in the respiration chamber, the metabolism was 50 per cent (beyond all reasonable expectation!) higher, there is still a surplus of apparently unexpended 35,000 Calories. Since the analysis of the dead animal shows that there has been no replacement of water by fat, the only alternative is to assume that this extra energy of 500 Calories per day must have been utilized in the production of heat for the body. But such an amount of heat would suffice to raise the temperature of the dog weighing 20 kilograms at least 30° C. The argument, therefore, would obviously reduce itself to an *ad absurdum*. The only plausible explanation of the fact is the one which Grafe avoids, namely, that the dog receiving superfluous quantities of food was unique in that he did not accumulate deposits of fat, but "worked off" the excess through restless activity. It is known, of course, that some animals, notably geese and swine, lend themselves easily to masting and fattening, but the horse grows very restless when overfed. Human beings are likewise of these distinct types, some "working off" all excess energy in various forms of activity, while others retain and store it up in their body as fat.

Müller's experiments are a direct antithesis to those of Grafe. Experimenting with a normal individual, he found that a diet excessively rich in nitrogenous substances had no effect upon the oxygen consumption even while large quantities of nitrogen are retained in the overfed organism. The subject of the experiment, a young student, received 1,023 grams of nitrogen, or 6,394

grams of protein, in the course of four weeks during which time the body weight increased by 4.6 kilograms. The largest increase occurred in the first two weeks. Apparently the retention of nitrogen did not result in the formation of flesh; at any rate as soon as the quantity of protein in the food was diminished the body commenced to lose nitrogen. Respiration experiments performed with this subject revealed no difference in the consumption of oxygen at any phase of the experiment, and Müller quite rightly concluded that "there is no increase in the gaseous metabolism corresponding to the accumulation of nitrogen."

The situation is quite different when the excessive amounts of nitrogen are actually used in the building up of the tissues. Müller understood this difference, and to verify his views he performed similar experiments with patients recovering from heavy sickness. "The sudden change from chronic undernutrition to normal nutritive conditions is accompanied by a rapid rise in the basal metabolism. This ensues at the same time as the nitrogen retention takes place, but there is no parallelism between the two. The increased metabolism is not, therefore, a direct result of a progressive acquisition of flesh, but of the generally enhanced metabolism of the protoplasmic substance."

CHAPTER VII

INTERMITTENT INANITION

The problem of the effect of repeated fasting upon the organism must be regarded as one of the least well understood in the province of inanition. In considering this problem two essential points must be borne in mind, namely, the duration of each fast and the interval between successive fasts. Evidently, the final outcome will be greatly affected by a variation in either or in both of these conditions. Is a brief fast, lasting about 24 to 72 hours, repeated from time to time of any particular benefit to the organism? Does such a periodic experience of mild fasting improve its vigor, resistance to disease and the functions in general? The hygienic significance of brief fasts prescribed by religious custom is very generally extolled, but what do we really know of their effect on the organism?

The experimental study conducted by Gorokhov, Vavilov and others on men who alternated a complete, mixed diet with one consisting of black bread (2 to 3 pounds daily) and tea only, throw little light on our problem. In the first place, these men did not actually fast during the three day periods but subsisted on a deficient diet consisting chiefly of carbohydrates. Little of any particular value has been brought out by these studies.

Von Seeland from his experiments with chickens claims that intermittent brief fasts conduce to greater development of the body. He used birds which already attained a constant body weight, and some of them he fed regularly every day while others were deprived of food from time to time for periods of one to two days. He discovered that the chickens thus periodically fasting became heavier than the control birds although they were actually getting less food than the latter. According to von Seeland the increase in weight was not due to deposition of fat, but to an accumulation of protein material, i.e., to an increase in flesh. No valid chemical evidence has been offered for this claim by von Seeland, who maintains that the periodic

fasting had the effect of making the body heavier, stronger and more solid.

Experimenting with salamanders (*Triton cristatus*) the author found that specimens which were fed intermittently neither became as heavy nor as large as the controls; that is to say, their growth has been retarded from the point of view of both increase in weight and in size, and that the frequently repeated starvation affected unfavorably the vitality of the organism. This conclusion concurred with that of Kagan who subjected pigeons two or three times to fasting, feeding them abundantly in the periods between. Kagan found that the power of resistance declined with each new experience of starvation. "The organism which recovered from inanition through the consumption of a liberal quantity of food still shows the effects of the previous experience . . . and when the inanition is repeated dies sooner than the normal organism" (p. 277).

While the experiments of Kagan as well as my own contradict the results claimed by von Seeland, this would not necessarily disprove his contention of an invigorating influence of brief fasts inasmuch as in our experiments the duration of each fast was considerably greater. However, Richet's experience with intermittently fasting rabbits likewise fails to corroborate von Seeland's findings.

The effect upon the growth of an organism serves as a good method for studying the question, and we may utilize this method in determining whether or not intermittent fasting is prejudicial to the animal's vitality and vigor. In the next chapter the broader implications of this method will be discussed more fully in connection with the problem of the relation between the amount of food consumed and the increase in body weight secured. It will suffice to say here that in the case of four groups of salamanders, each comprising four individuals, which have been subjected to intermittent inanition, the increase in body weight for a definite length of time was 57 to 81 per cent of that found in the control salamanders. Since the amount of food consumed in that time was approximately only 50 per cent of the quantity obtained by the regularly fed control animals, it is evident that a greater proportion of the nourishment was utilized for growth, but that the intermittently fed salamanders have fallen considerably below the level attained by the controls. Taking the average for all four groups together, we find that the

intermittently fasting specimens with one-half the amount of food reach somewhat more than two-thirds of the body weight of the continually fed salamanders.

These results are obviously at variance with those of von Seeland who maintains that his periodically fasting birds have done best. The difference in our results may, of course, be accounted for on the assumption that the periods of fasting for the salamanders have been rather long (one week), which would apply equally to Kagan's experiments with pigeons, while von Seeland's chickens never fasted more than 12 to 48 hours at any time. It is possible that the detrimental effect of the intermittent inanition is caused by extensive changes in the composition of the organism which remain even when the animal's weight has been brought back to the original level. One may think, of course, of the increased water content of the tissues, and this may be the cause of the lowered resistance to repeated inanition. Very brief fasts naturally would not have the same effect upon the composition of the tissues. It is, therefore, most desirable to extend these studies, varying the two essential conditions, as was already pointed out at the outset.

PART IV

INANITION AND GROWTH

INANITION AND GROWTH

Growth, like development, is a fundamental property of all living substance. The simplest conception of growth is that of an increase in size and weight, and the organism's growth from this point of view would have much in common with the growth of a mineral crystal. But an increase in bulk is not identical with growth. Occasionally an organism or certain parts of it may increase through absorption of water, as happens in edema. It is obvious, however, that the edematous organism is not growing. Likewise, there may be a considerable increase in weight due to an accumulation of fat without any active growth.

Growth must necessarily lead to morphological change or development. The form of the organism is a function of time, being determined by the specific rates of growth of its separate parts. When growth is most intense developmental changes are also very rapid as, for instance, in the young. But growth is more fundamental than development. An organism does not grow as a whole in the sense that it increases at a uniform rate in all its parts. From the viewpoint of growth the organism may be more properly regarded as a mosaic. In the early stages of development the growth activity of the nervous system predominates and as a result the embryo is chiefly brain. In the newborn the head is relatively the largest part of the organism and in the subsequent years of growth it undergoes little change in size. This uneven growth accounts for the fact that the proportions of the body are continually changing as the individual passes through the stages of infancy, childhood, adolescence to the adult and finally to the aged condition.

An increase in size or mass is the most obvious manifestation of organic growth, but as a cellular function it comprises three fundamental processes: cell multiplication, cellular enlargement, and the accumulation of intracellular and intercellular substance. In normal growth these three processes are coördinated, but neither process alone can be identified with normal growth. Active cell proliferation may occur as in the connective tissue

hyperplasia replacing degenerated parenchymatous cells; or at times there may be excessive enlargement of the cells of an organ or an unusual accumulation of non-protoplasmic material inside and outside the cells. Much as either of these phenomena may represent an exacerbation of one or another of the fundamental growth processes, they are unlike the ordered growth of an organism—they are pathological phenomena of hyperplasia, of hypertrophy and infiltration. Normal growth presupposes the balanced adjustment of all three processes.

We are entirely ignorant as to the nature of the force which impels an organism to grow. We know that the growth impulse is deeply rooted in the composition of the organism, that it is an inherent force. The individual, sexual, racial differences in growth activity are familiar. The ductless glands, especially the hypophysis and the thyroid, form a truly remarkable chemical mechanism for regulating growth and directing the impulse towards an orderly and well proportioned result. Temperature and climate are also of great importance, but the greatest influence among the external factors belongs to nutrition. The growth capacity is determined by heredity and while there is no evidence that it can either be increased or completely repressed, it is subject to limitation through nutritional influences which give free scope or hold in check the organism's inherent impulse to grow. The growth impulse requires material which can be molded into new tissues, and nutrition vouchsafes the organism this building material. When nutrition is interrupted, as in the case of starvation, or when the building material is deficient either in amount or in quality, as in the various instances of undernourishment, growth is likewise seriously interfered with. But even under such circumstances the cessation of growth may be entirely deceptive. While the organism as a whole may diminish in weight, and while the reserves of the tissues may be lavishly drawn upon to supply energy for the maintenance of the insufficiently nourished organism, growth activity is not necessarily extinguished but only limited and reduced in its extent.

Judging by gross changes in body weight alone, growth is suspended not only in complete inanition but also in partial inanition and in undernutrition. It is a well known fact that the most essential building material for the organism are the proteins. The proteins are made up of a variety of simple compounds, the amino acids, and differ from each other by the rela-

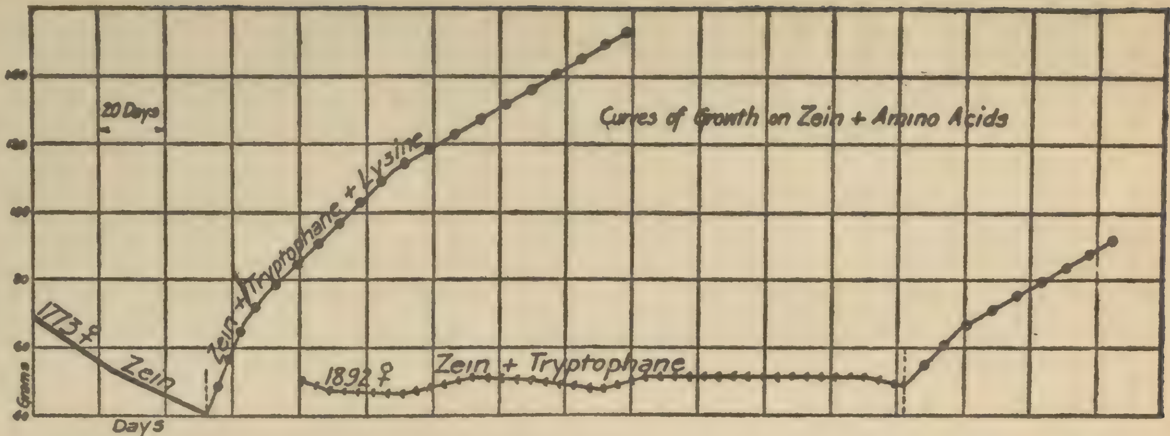

FIGURE 12.—Curves showing the effect of the addition of tryptophane and lysine to zein which does not contain these amino acids. The addition of the tryptophane permits maintenance without growth when zein is the sole source of protein. The addition of both tryptophane and lysine to zein enables the rats (see curve for rat 1773) to make considerable progress. It is interesting to note that the capacity to grow is not lost by prolonged dwarfing resulting from imperfect diet as shown by rat 1892. After its growth had been inhibited for six months it resumed growing very rapidly when lysine was supplied to the diet containing tryptophane and zein. (After T. B. Osborne and L. B. Mendel.)

tive amounts as well as the kinds of amino acids composing their molecule. The protein of the organism is synthesized from the amino acids of the food proteins. The organism possesses only a limited ability of synthesizing the amino acid radical from simple components. It cannot, for instance, build up lysine nor cystine nor can it synthesize such aromatic compounds as tyrosine, phenylalanine, or tryptophane. These amino acids must of necessity be furnished in the diet. It was a great contribution to the intimate understanding of the growth problem when Osborne and Mendel demonstrated that the quality of the protein plays an important rôle in securing normal growth, and that certain amino acids were absolutely necessary for the purpose.

With a mixed diet containing proteins of various composition there is no danger of suspension of growth from lack of some specific amino acid. But this danger becomes a reality when the protein of the diet is of only one kind. Thus, for instance, proteins like zein or gelatin lack both tryptophane and lysine, and cannot sustain growth. In fact, animals whose diet contain zein or gelatin as the sole source of protein will actually lose weight. The growth capacity apparently is not affected because the animals resume growing as soon as the missing amino acids are supplemented. Even after many months of repression, the growth impulse suffers no injury, and the animals commence to gain weight quickly on adding the indispensable amino acids. This is clearly shown by the graphic records of the changes in body weight of the rats fed on isolated proteins. On adding tryptophane to a diet containing zein as its exclusive protein component nutritive failure and a progressive decline in weight can be forestalled. The rats remain in a state of equilibrium, neither gaining nor losing weight. The addition of lysine, the other missing amino acid, is required to start up again active growth. Likewise, when the protein edestin, which is poor in lysine, or the protein casein, which has little of the sulfur containing amino acid cystine, are the only source of protein in the diet, large quantities of these must be consumed in order to provide sufficiently of these acids to insure normal growth. Where this condition is not fulfilled, growth will be defective. The specific nature of the deficiency can be demonstrated by adding the particular amino acid to the diet, when the condition is remedied quickly and with certainty.

In the chapter dealing with partial inanition it has been pointed

out that vitamin deficiencies invariably affect growth. Diets of an adequate energy content and proper qualitative composition fail to sustain growth activity when vitamins are absent. Considering that the vitamins are present in extremely minute amounts, the influence exerted by them on the growth impulse is almost miraculous.

As an external factor nutrition is the most important, giving free scope or holding in check the inherent growth impulse of the organism. The rate of growth fluctuates with the nutritional régime. The growth capacity is determined by heredity and there is no evidence that it can be increased by outside influences. Uhlenhuth[1] by feeding Amblystoma on anterior lobe of hypophysis exclusively produced salamanders of unusually large size. Notwithstanding these results it is doubtful in the highest degree if he demonstrated the possibility of artificial giantism, as he seems to think. The experimental procedure involving the exclusive feeding of earthworms to the control salamanders and of hypophysis to the experimental animals is open to very grave objections. No evidence of any kind is given to show that the different diets are really equivalent in point of view of energy content or qualitative composition apart from any specific substance which the hypophysis presumably supplies. The choice of salamanders for this purpose is likewise unfortunate because these animals are of the indeterminate type of growth, continuing to grow all through their existence. There is, of course, no assurance that either the laboratory animals fed on earthworms or those found in nature have the optimum conditions for growth. It seems, therefore, entirely unwarranted to regard these results as evidence that the growth impulse may be so modified experimentally as to produce giants.

On the other hand, careful experiments have shown beyond a doubt that the growth capacity of an animal can neither be destroyed nor even lowered. When the nutritive condition, or the environmental condition in general, is rectified, growth at a greater tempo at once occurs and, despite prolonged inhibition of growth, full size may be reached. Shapiro retarded and even brought to complete standstill the growth of kittens by chloroforming them twice daily. As soon, however, as this treatment was discontinued growth activity was renewed with even greater vigor so that in the next period the stunted kittens would catch

[1] *J. Gen. Physiol.*, 3, 351, 1921.

FIGURE 13.—The rations of these two rats from weaning time were exactly alike except in the character of the fat which they contained. The one on the left was given 5 per cent of sunflower seed oil. The one on the right was given 1.5 per cent of butter fat. Butter fat, egg yolk fats and the leaves of plants contain a dietary essential, the chemical nature of which is still unknown, which is necessary for growth or the maintenance of health. This substance is known as the fat-soluble vitamin *A*, and is not found in any fats or oils of vegetable origin. A lack of this substance in the diet causes the development of a peculiar eye disease known as xerophthalmia. The rats were of the same age when photographed. (From E. V. McCollum's *Newer Knowledge of Nutrition*. Courtesy of The Macmillan Company.)

up again, as far as weight is concerned, with the control animals. The retardation, holding the growth impulse in check, is only temporary, and, as soon as this check is removed, is compensated by accelerated growth. In like manner, animals stunted experimentally through underfeeding are not robbed of their inherent growth power. When favorable conditions are restored they grow quickly to the normal level. This, at any rate, is the case with mice and rats which have been studied extensively from this standpoint. Both Miss Ferry and Miss Wheeler observed that after a prolonged period of stunting an increase in weight more rapid than normal takes place. In other words, the stunted animals grow at a rate which is characteristic for their small size but not for their advanced age. The rate of growth, therefore, seems to be primarily a function of size rather than of age.

Aron, on the other hand, found that if the stunting of rats is continued until an advanced age the animals will no longer attain normal size, though they increase in weight and in stature with the improvement of their nutrition.

The testimony of the anthropologist is not so encouraging. Boas who made an extensive investigation of the growth among children of different social strata comes to the following conclusions:

"It seems very likely that the abnormally large amount of energy expended upon rapid growth during a short period is an unfavorable element in the individual development. A study of the phenomena of growth of various groups of the same population has shown that early development is a concomitant of economic well-being, and that a characteristic of the poor is the general retardation in early childhood, and the later rapid growth. It follows from this that there is a corresponding, although not equal, retardation in early mental development, and a crowding of developmental processes later on, that probably place a considerable burden on the body and mind of the poor, which the well fed and cared for do not bear. The general laws of growth show also that a retardation kept up for an unduly long period cannot be made up in the short period of rapid growth; so it would seem that, on the whole, excessive retardation is an unfavorable element in the growth and development of the individual. Whether there are similar disadvantages in a considerable amount of early acceleration is not clear."

The influence of social position on the growth rate is shown in

the diagram, Figure 14, which is a graphic record of the average weight and height of German children of different ages. Since the children attending the public schools come from the poorer strata of the population, while those of the gymnasiums belong to the middle and better-off class, the curves show unmistakably the difference in growth of the children reared in different economic environments. These records pertain to the children of Germany before the war, that is, when she was at her best. It is seen from this figure that the middle class children at every age show a distinct advantage over their fellows belonging to the less fortunate social grouping.

The difference apparently remains permanent as the following data of the stature of workingmen and students of the same age indicates: [1]

	Stature in Cm.	
	Student	*Workman*
Italy	166.9	164.4
France	168.7	164.4
England	172.4	169.8
Spain	163.9	159.8

We shall consider later the probable cause of the detrimental effect of a too prolonged inhibition of growth. It is important to point out here that the reëstablishment of the normal weight does not indicate unmistakably that the organism is normal in every respect. This at any rate is the conclusion one may draw from Hatai's experiments on rats. He stunted rats 30 days old by feeding them exclusively on starch. The rats were kept on this insufficient diet for 21 days. They did not take on weight and remained much smaller than the control rats (55 to 60% lighter in weight) and showed other symptoms of inanition, such as curvature of the back, unsteady movements, rough fur, dry skin, partly closed eyelids. We now recognize this syndrome of symptoms as resulting primarily from vitamin deficiency. When after 21 days of this régime their nourishment was again improved the animals recovered with marvellous celerity. The effect of the stunting quickly disappeared and was eventually completely compensated so far as the weight of the body or that

[1] Martin, 1914, *Lehrbuch der Anthropologie,* Jena. Cited after Lipschütz.

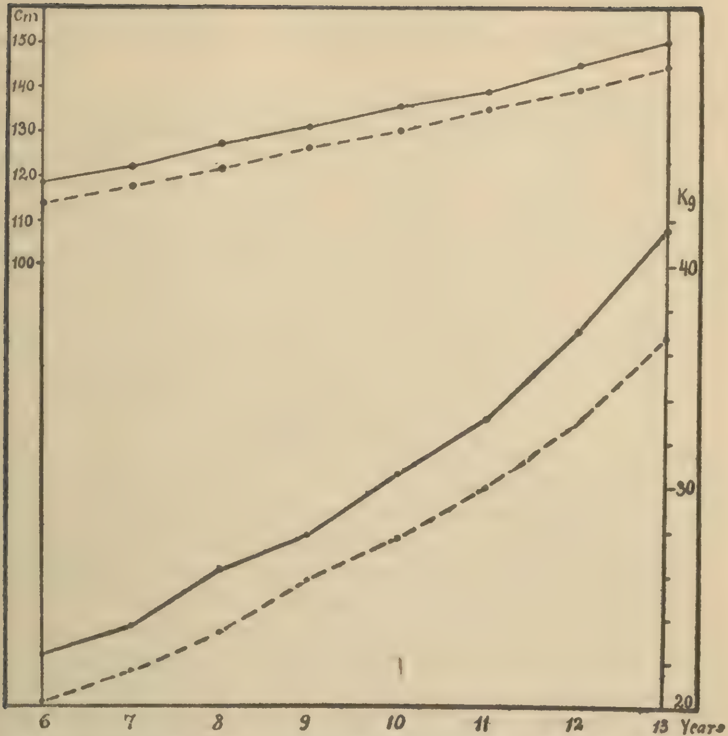

FIGURE 14.—A series of curves showing the progress both in body weight and in body stature of boys between the ages of 6 and 13 years. The broken line curves represent the growth of pupils from public schools while the solid line curves are of pupils of the gymnasiums in Berlin. The boys attending these schools come from different social classes. (Based on data from Mosse-Tugenreich's *Krankheiten und sociale Lage.* München, 1912.)

of the central nervous system was concerned. The study of the chemical composition of the animals showed that the growth curve alone is rather misleading, for while their weight was now normal for their age they were not entirely free from the stigma of the partial inanition. Their brain and spinal cord had a higher per cent of water and a lower per cent of alcohol-ether extractives (lipins).

The evidence thus far adduced shows that the growth impulse cannot be destroyed though its operation may be hindered or even completely suspended. But does growth activity actually cease? What happens when a young growing organism is given a diet just barely sufficient to provide for replacement of the wear and tear, and the maintenance energy requirement of the organism? What happens in the growing organism when there is no provision for its growth activity? Judging by the gross body weight which under the circumstances does not change and remains practically stationary one would be led to conclude that growth has in fact been brought to a stop. Experimental investigation, however, demonstrates the utter fallacy of the assumption, because the organism does not grow as a unit. It is a mosaic of interrelated parts each, however, having its own growth history. The growth curve of one portion of the organism may be ascending while that of another has already reached the peak of its growth or indeed is on the downward course. Furthermore, the growth impulse of one may be great and that of another feeble. At times of plenty when there is enough nutriment to furnish building material for every part of the organism the gross increase in weight is a good measure of the resultant growth. But it obscures the essential fact of the composite nature of the growth phenomenon. Waters' experiments with growing calves and Aron's work on dogs illustrate this idea. These investigators discovered independently of each other that through chronic underfeeding they could keep young animals at a constant body weight but could not bring about complete standstill of the growth process. The part of the organism which at that phase of development possesses the strongest growth impulse is potent to attract to itself whatever building material is available, and this not sufficing will even encroach upon the reserves of other tissues. We witness, therefore, cataplasia or reduction of certain parts of the organism alongside with a progressive building up, or euplasia, of others. Such a condition has already been shown to

exist in the salmon during the spawning season when these animals take no food sometimes for several months, and while all organs and especially the muscles are used up in furnishing energy to the starving salmon, their gonads grow and develop luxuriantly. The young calves and dogs, whose diet was thoroughly adequate in quality but not enough in amount, continued to grow though retaining a constant weight, but the growth was limited only to the skeleton. This increased both in size and in mass, and as a result the animals actually grew in stature. Even the muscles were depleted of their stored material to satisfy the growth impulse of the skeleton, and the animals were gaunt, lean and disproportionately narrow. If age is merely a stage of growth, as has been suggested before, it would be necessary to conclude that the different organs of the organism may represent different ages if their growth has been unequally suspended. This is an opinion which both Aron and Waters seem to draw from their observations. Aron noted that the voice of his dogs was distinctly that of young puppies in spite of their advanced age and large stature. Waters likewise found that the flesh of the underfed calves retained the tenderness of a young animal though according to their age it should have had the characteristics of beef.

These experiments of Aron and Waters are very important theoretically because they give much weight to the idea that growth is really independent of food in the sense that one is not the cause of the other. We shall dwell more fully on the relation between food supply and growth later on. At this junction we will develop further the idea that the growth impulse of a particular part of the organism may be sufficiently puissant to draw to itself nutriment and to infringe upon the reserves of the less active tissues and cause them to undergo cataplasia.

Perhaps the best demonstration of this is afforded by the study of regeneration. Regeneration is a common occurrence in all organisms, though the regenerative capacity varies greatly among different animals and different organs and tissues of the same animal. Lower organisms are frequently endowed with marvellous regenerative powers, being able not only to repair small damage but also to replace complete portions of their body or complex organs like the limb or eye when these are accidentally lost. Crustaceans can regenerate lost claws, legs, tentacles or eyes; salamanders can regenerate limb, eye or tail when deprived

FIGURE 15.—A photograph of two dogs at the age of 350 days. Up to the age of 40 days the two puppies were brought up under similar conditions and at that age their weights were practically the same, about 2,000 grams. From this time on, however, one puppy was given a sufficient diet consisting of 400 to 680 Calories per day (the daily Calories being adjusted according to the changes in body weight), while the other received 110 to 175 Calories a day. The former increased from 2 to 6.4 kg. in this interval of 310 days, but the other retained practically an unchanged weight (increased only 400 grams). Up to the 200th day it became thinner, taller and longer but afterwards showed little change in appearance. Although it was not much more than skin and bones it was vivacious and even more active than its mate which was three times heavier. This dog gained weight rapidly when after 350 days it was again fed plentifully, as can be seen from the second half of the picture taken at the end of 500 days. (After Aron.)

of these appurtenances in the life battles or at the hand of an interested experimenter; likewise lizards habitually leave their tails with the disappointed pursuer and later acquire a new tail by regeneration. Now, it is a remarkable fact that the starving organism does not lose its regenerative power. An organism already much emaciated through prolonged inanition will draw upon its scanty reserves in the effort to renew a severed part of its body. The little flat worms, *Planaria,* commonly found in stagnant waters, possess an extraordinary regenerative capacity. Morgan has shown that even in advanced stages of inanition, when the Planarian has been reduced to a small fraction of its original size, the regenerative impulse is still sufficiently strong to reduce still further the much depleted tissues in rebuilding parts of the body which have been cut off. Of course, during inanition the missing organ does not regenerate as rapidly or as fully as in a well-fed animal. The important thing, however, is that inanition does not deprive the organism of its inherent regenerative impulse. Nourishment, when this is given, merely increases the scope of its activity. Experimenting with salamanders, *Triton cristatus,* the author found that starvation did not interfere with the regeneration of the tail which has been cut off. The tails grew slower than in the control animals which were abundantly fed. When, after several weeks of starvation, the salamanders having in the meantime lost one-fourth of their original weight, they were fed once more, the regeneration of the tails was immediately improved and in course of time attained or even exceeded in length the tails which were cut off.

It has been repeatedly emphasized that just as soon as an animal, which through acute or any other form of inanition lost weight, is given proper nourishment it commences to grow at a spectacular rate and in a comparatively brief period regains all it had lost or even increases beyond the original level. The rapid gain in weight is a manifestation of a vigorous process of growth. There is not merely an accumulation of reserve substance, but a true growth in the sense defined previously. There is prolific cell multiplication, great expansion of the cells and a reaccumulation of reserves in the form of intracellular and intercellular deposits of products of their metabolism. Nitrogen is retained with an avidity characteristic of the young growing organism. Frequently, in a short span of time, an increase of the body mass is accomplished, which required years of normal

growth to bring about. The inanition has produced a rejuvenation of the organism. In our study of the histological phenomena accompanying inanition it has already been learned that except in the advanced stages there is scarcely any evidence of tissue degeneration. On the contrary, the cells remain intact though they lose a large portion of their substance. In the keen competition which reigns in the organism subjected to inanition the weaker and less essential parts of the cellular organism are sacrificed first, just as we have seen this to happen to the less essential parts of the entire organism. The more vital parts remain and the vitality of the cells and their vigor is thereby improved. This seems to be the rationale of the invigorating and rejuvenating effect of inanition. Biologically speaking, though the organism acquires no new assets it becomes stronger by ridding itself of liabilities. In the foregoing (see p. 200) it has been pointed out that the cell-nucleus ratio in inanition changes in such a manner as to increase the preponderance of the nucleus. Morphologically, therefore, the cells composing the organism assume a youthful condition. They resemble more the embryonic cell in this respect, and this may account for the expansive growth which they display under the proper nutritive régime.

Unfortunately this phenomenon of intensive growth following inanition has not been studied as much as its intrinsic importance would warrant. Pugliese made a few interesting observations on the changes in composition of the liver and muscles in dogs which received food for four days after a prolonged fast (loss in body weight about 35%). The ash content of the liver increased considerably during the fast, from 3.40 per cent of the dry liver substance to 4.56 per cent. This increase is undoubtedly due to destruction of erythrocytes and retention of the iron salts in the liver. As soon as feeding is resorted to the percentage of ash returns again to the normal level. It may be assumed that the iron accumulated in the liver is carried off and utilized in the regeneration of the red blood cells. In the muscles the water content, which on a fat-free basis increased from 73 to 80.4 per cent during inanition, still remains high though after four days of feeding it is only 79.8. The amount of fat in the muscle increases quickly, by more than 0.5 grams per hundred grams of substance. The building up of the muscle is also seen in the rising content in nitrogen. On a water and fat-free basis the nitrogen content of the muscles diminished from 14.5 per cent to

14 as a result of inanition. After four days of feeding this has already risen to 14.2. The ash of the muscle substance (also calculated on a fat and water-free basis) having diminished from 5.36 to 5.03 per cent shows a distinct tendency of returning to the original level.

The author studied the effect of refeeding on the histological characteristics as well as the composition of the salamander (*Diemyctylus vir.*). The changes in the histological picture have already been described (see pp. 200-204). The salamanders starved 125 days. They lost 42 per cent in weight, and their body length diminished on the average from 94.3 to 91.5 millimeters. The salamanders were now fed on beef, the amount of meat consumed being carefully recorded. In the course of eight days of liberal feeding they gained about 44 per cent in weight and the original body dimensions were nearly restored (94 mm.). The investigation has further disclosed the rather remarkable fact that although the average amount of food consumed in those eight days was only 0.531 grams, the actual gain in body weight was 0.651 grams. An examination of the chemical composition of the refed salamanders shows immediately the cause of this apparent discrepancy.

	Composition of the Salamanders			*Difference*	*Per Cent of Gain or Loss*
	Before Inanition	*After Inanition*	*After Feeding*		
Body weight..	2.5560 Computed	1.4827 Computed	2.1335 Found	+0.6508	+43.9
Dry substance.	0.6436	0.3517	0.4397	+0.0880	+25
Water	1.9124	1.1310	1.6938	+0.5628	+49.8
Organic subst..	0.5558	0.2418	0.3366	+0.0948	+39.2
Ash	0.0878	0.1099	0.1031	—0.0068	—6.2

It is clear from the analytical data that practically all the constituents of the organism have grown, though at different rates, in the eight days of refeeding. The mass of dry substance has increased much less than the total body weight, while the water content has increased considerably more. During realimentation the organism retains much water, which accounts for the fact that the gross gain in weight exceeds the quantity of food consumed.

Further experiments performed with the salamander (*Triton cristatus*) demonstrated that the growth impulse and not the

quantity of consumed food plays the leading rôle. These experiments substantiated the idea that growth which ensues after a preliminary inanition is not unlike embryonic growth in its intensity. It is well to bear in mind that the reduced size of the cell, or rather the altered cell-nuclear ratio, is probably in some way responsible for the vigorous growth process, and that the rejuvenescence of the organism is dependent upon this condition. Many years ago Kagan observed that following 17 days of complete inanition rabbits gained 56 per cent in weight on a diet which could just barely maintain a state of equilibrium in the normal condition. The retention of protein by the cells as the chief material for building up the protoplasm is much greater than under ordinary circumstances, and along with this goes also a retention of water.

Comparing the amount of food consumed for a certain length of time with the gain in body weight for the same period, we obtain a ratio which serves as a coefficient of growth. When the two quantities are equal, the coefficient $\frac{G}{F}$ is, of course, one; when the gain in weight is less than the amount of food consumed the coefficient is a fraction which has a greater value the larger the proportion of food utilized for purposes of actual growth. In a number of experiments both with regularly fed (control) salamanders and those which have been fed after a preliminary period of inanition, it was found that the coefficient of growth for the former was only 0.26 while for the latter it was 0.73 (average for seven days). Furthermore, the increase in body weight over a long time was compared for these two sets of animals and it was found that with half as much food consumed the salamanders that had once starved attained a weight which was, on the average, one per cent above the weight of the controls. This was made possible by the fact that the rate of growth of the previously starved salamanders was twice as great as that of the control animals.

The idea which the author developed in his investigation on the salamanders received further conformation in the splendid work of Thompson and Mendel who carefully determined the amount of food eaten by albino mice which have either been regularly nourished or stunted by previous underfeeding. These investigators reached the same conclusion, namely, that "in all cases the weight gained by the experimental, i.e., the stunted,

animals was greater in proportion to the food eaten than that gained by the controls. . . . Comparisons of the economy of the food intake show that the gain of weight during the period of acceleration of growth following suppression is ordinarily accomplished on a smaller intake of food than is ingested during a period of equal growth at normal rate from the same initial weight. The advantage of this apparently better appropriation of food during accelerated growth may actually be sufficient, in some cases, to offset the added expense of the food required for maintenance without growth during a brief preliminary period of suppression."

This discussion has revealed that the effect of inanition in producing suppression of growth or actual decline is not a serious menace, if not carried too far, and that proper nourishment quickly restores the organism to its normal state. This is a very encouraging aspect of inanition, and is a good prognostic sign in all diseases where a fundamental undernourishment is the cause of extensive wasting of the body. It is needless to say that no sensible clinician would attempt to build up an organism by forced nutrition, because the most that he could accomplish with much effort is to burden the body with deposits of inert substance. The situation is entirely different with patients who have either emerged from a wasting disease and are reconvalescing, or those who through a combination of circumstances have become the prey of chronic undernutrition. Here the opportunity for building up new tissue is offered to the clinician who understands how to avail himself of the growth impulse. The results obtained under these conditions are frequently astonishing. Kissling's report on the application of the Lenhartz diet for patients who have been debilitated through undernutrition is an added testimony of the wonderful recuperative power of the organism. From a large number of case records which he discusses a few are chosen by way of illustration of the aid which the keen clinician can obtain from the inherent impulses in building up a debilitated body. Here is an instance of a man 41 years of age, well beyond the period of normal growth. As his weight shows, 44 kilograms, he is greatly undernourished. Liberal nourishment together with complete bodily rest, and as little medication as possible, built up his weakened organism and in seven weeks' time he acquired 18 kilograms, an increase of 41 per cent. Another man, 22 years old, gains 43.7 per cent in weight in 52 days. A girl 19, weighing

only 39.5 kilograms, gains in one month 26.6 per cent in weight, etc. And as the body is being gradually built up the disease which has lodged in the weak frame also yields to the rejuvenating influences of the renewed growth activity.

When one turns from the experience of the laboratory to the wider field of observation, to human society, one is confronted with new questions: what hope is there for the children whose growth has been retarded through unfavorable conditions? what is the relation between retarded growth and the attainment of normal development? It is important in approaching these problems to realize first of all that the retardation of growth in young children is usually associated with a complexity of circumstances unknown in most laboratory experiments. Prolonged retardation of growth among children is not merely an effect of undernourishment but of poverty, and poverty is a social and not a nutritional condition. Poverty means poor nourishment but it spells in even bolder type: squalor, putrid air, want of hygiene. Like poverty, retarded growth is therefore a sociological problem. It usually results from the most insidious form of deficient diet—malnutrition.

Stationed with the American Expeditionary Force at Trier, Germany, Blanton made a special study of the effect of malnutrition on the school children of that region. War conditions in general and the poor and insufficient food were responsible for the marked lowering of scholarship, and even pupils who before the war did superior work did but average work then. The examination of the physical condition of the children throws some interesting light on the causation of this lowering of the standard. In 40 per cent of the children Blanton found evidence of loss of nervous energy directly traceable to malnutrition, and this was associated with an increase in the number of border line defectives of about one per cent of the total school population. The malnutrition produced a retardation which extended also to the finer processes of nervous coördination involved in good speech. There has been a marked increase in the number of children with poor, lisping, slurring speech. The specific changes noted in the children and caused by malnutrition were: lack of nervous and mental energy; inattention and general nervous restlessness during school hours; poor comprehension and poor memory for school work.

Blanton furthermore found that more than five per cent of the

total school population suffered injury to the nervous system such as to affect the intelligence permanently. It is true that Blanton attributes the resistance to the blighting influence of malnutrition to the nervous strength and intelligence of the original stock. When one recalls, however, that children received at orphan asylums and other charitable institutions, coming from strata of society where existence has always been more or less precarious, were generally about 30 per cent below standard weight, it seems at least reasonably doubtful if the five per cent of permanently injured in intelligence children are necessarily of tainted heredity. Malnutrition of some degree is invariably associated with poverty, and poverty did not originate with the World War but has merely become more extensive under its impetus. It is only natural that those whose physical stamina had been undermined even before the war should have crumbled under the additional strain of war-time parsimony and want.

Not only retarded bodily growth but mental inferiority as well may thus be the result of undernourishment. The rapid progress in regaining weight has been shown, for instance, by Goldstein who investigated over 500 children in the special hospitals for the war-time victims in Berlin. There is no information available on the equally important problem of the mental recuperation of these children. The experiments of Hatai on rats which, after a period of malnutrition, have regained normal weight on a full diet but nevertheless showed a profound alteration in the composition of their nervous system have a very significant bearing upon the problem. Although there is no valid proof, evidence is not lacking that at least in part mental inferiority may be traced to defective nurture rather than to poor nature. It would be invaluable to discover whether any of the feeblemindedness charged against tainted heredity may not in reality originate from inadequate nutrition.[1] With the wonderful recuperative power inherent in the organism, what an opportunity for the sociologist and the social worker to reclaim the derelicts and to restore them to a wholesome existence.

[1] "There is a growing impression that a good deal of feeblemindedness and insanity are environmental rather than hereditary traits; poverty, malnutrition, and especially syphilis are said to play a considerable rôle in their production. It is unsafe, therefore, to conclude that the human germ-plasm is as badly contaminated as some pessimists seem to think." T. H. Morgan in the 1922 Middleton Goldsmith Lecture on "Some possible bearings of genetics on pathology."

The condition portrayed for Germany immediately after the war is not limited to that country alone. What happened there *en masse* is more or less a chronic state of affairs in every country only on a different scale. Malnutrition of children is not uncommon in this country either. Taking a single example, Miss Brown in her survey of one school in Kansas attended by children of an American wage earning community, found severe malnutrition prevalent among them so that on the introduction of the protective feeding plan the specially fed children gained as much as 300 per cent over the control group in the same school. At the same time, the intensive feeding and health service plan brought other fruit as well, and in a short while the school which for scholarship ranked lowest in the city attained third place.

Both the experiences of the biological laboratory and of the laboratory of life confirm the view expressed in this discussion, namely, that the organism possesses truly remarkable recuperative ability, and these experiences should serve as guide and inspiration as well as a measure of the social responsibility.

PART V

BIBLIOGRAPHY

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